PB80-208788

# Chemical Hazard Information Profiles (CHIPs)

(U.S.) Environmental Protection Agency
Washington, DC

Apr 80

U.S. Department of Commerce
National Technical Information Service
NTIS

## TECHNICAL REPORT DATA
*(Please read Instructions on the reverse before completing)*

1. REPORT NO.
EPA 560/11-80-011

2.

3. RECIPIENT'S ACCESSION NO.
PB 80 208788

4. TITLE AND SUBTITLE
Chemical Hazard Information Profiles (CHIPs)
August 1, 1976, to November 20, 1979

5. REPORT DATE

6. PERFORMING ORGANIZATION CODE

7. AUTHOR(S)
Chemical Hazard Identification Branch/Assessment Division/OTE/OPTS/EPA

8. PERFORMING ORGANIZATION REPORT NO.

9. PERFORMING ORGANIZATION NAME AND ADDRESS
Same as box 12.

10. PROGRAM ELEMENT NO.

11. CONTRACT/GRANT NO.

12. SPONSORING AGENCY NAME AND ADDRESS
Office of Pesticides and Toxic Substances TS-792
U.S. Environmental Protection Agency
401 M. Street, S.W.
Washington, D.C. 20460

13. TYPE OF REPORT AND PERIOD COVERED
8-1-76 to 11-20-79

14. SPONSORING AGENCY CODE

15. SUPPLEMENTARY NOTES

16. ABSTRACT

This collection of 40 Chemical Hazard Information Profile (CHIP) reports was prepared by the Office of Pesticides and Toxic Substances (OPTS) between August 1, 1976, and November 20, 1979. Chemicals are chosen for CHIP preparation on the basis of information indicating potential for adverse health or environmental effects of significant exposure. The CHIP itself is a brief summary of readily available information concerning health and environmental effects and exposure potential of a chemical. Information gathering for a CHIP is generally limited to a search of secondary literature sources and is not intended to be exhaustive; however, in depth searches on specific topics may be done on a case-by-case basis. In general, no attempt is made to evaluate or validate information at this stage of assessment.

Preparation of a CHIP is part of the first stage in the OPTS Chemical Risk Assessment Process. The purpose of the CHIP is to enable OPTS to make a tentative decision on an appropriate course of action for the subject chemical and to identify and characterize problems that may require more thorough investigation and evaluation.

17. KEY WORDS AND DOCUMENT ANALYSIS

| a. DESCRIPTORS | b. IDENTIFIERS/OPEN ENDED TERMS | c. COSATI Field/Group |
|---|---|---|
| | | |

18. DISTRIBUTION STATEMENT

19. SECURITY CLASS *(This Report)*

20. SECURITY CLASS *(This page)*

21. NO. OF PAGES

22. PRICE

EPA Form 2220-1 (9-73)

PB80-208788

August 1976 - August 1978

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

EPA 560/11-80-011
APRIL 1980

# CHEMICAL HAZARD INFORMATION PROFILES (CHIPs)

August 1976 - August 1978

Office of Testing and Evaluation
Office of Pesticides and Toxic Substances
Washington, DC 20460

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES AND TOXIC SUBSTANCES
WASHINGTON, DC 20460

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# Foreword

Evaluations of chemical substances prepared by scientists in EPA's Office of Testing and Evaluation, Office of Pesticides and Toxic Substances (OPTS), to implement provisions in the Toxic Substances Control Act (TSCA), will be published periodically and made available to the public in the TSCA Chemical Assessment Series. Some of the volumes in the series are reports on single chemicals; others are compendiums of information received and evaluated by the Agency about many chemicals. (The anticipated frequency of publication will vary among titles: some will be published annually, some semiannually, and others quarterly.)

Because the chemical assessments published in this series often will reflect initial or intermediate steps in EPA's evaluation of a chemical under TSCA, the Agency welcomes the submission of additional information for or comments on its evaluations. Such submissions will be considered either at a subsequent step in the assessment of the subject chemical or in the decision not to proceed with further evaluation.

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U.S. Environmental Protection Agency
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Generally, five thousand copies of each volume will be printed. When this supply has been exhausted, copies can be purchased from the National Technical Information Service (NTIS), whose "PB" reference number can be found in the OPTS "Comprehensive List of Scientific and Technical Reports," also available from IAO.

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# Introduction

This volume is a collection of forty Chemical Hazard Information Profile (CHIP) reports on 43 chemical substances or categories of substances prepared by the Office of Toxic Substances* between August 1, 1976, and November 20, 1979. Each CHIP report has been reviewed by OPTS staff, and a tentative course of action for further consideration of the subject chemical has been selected and documented in the CHIP report.

Comments are sought on the accuracy and completeness of the information contained in the CHIP reports and on the tentative dispositions. (See the Foreword for details on submitting comments.) All comments received will be available for inspection and copying in the OPTS reading room,+ unless specifically claimed as confidential in accordance with applicable EPA rules and procedures (see 40 CFR Part 2 [41 FR 36902, September 1, 1976]).

Readers and commenters should be aware of the intentionally limited depth of CHIP reports and of their role in the process of chemical risk assessment conducted by OPTS. Chemicals are chosen for CHIP preparation on the basis of information indicating a potential for adverse health or environmental effects, along with evidence of significant commercial production or environmental exposure. Such information may come from a variety of sources, including official submissions to EPA, scientific articles in the open literature, government reports, scientific papers presented at meetings, and recommendations from the public.

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*The Office of Toxic Substances (OTS) became the Office of Pesticides and Toxic Substances (OPTS) on October 19, 1979.

+Room E447 at EPA Headquarters, 401 M Street, S.W., Washington, D.C. 20460.

The CHIP itself is a brief summary of readily available information concerning the health and environmental effects and exposure potential of a chemical. Information gathering for a CHIP is generally limited to a search of secondary literature sources such as computerized data bases, abstracts, government reports, scientific review documents, and reference works. The literature search for a CHIP is not intended to be exhaustive; however, in-depth searches on specific topics may be done on a case-by-case basis. Relevant literature is usually reported in the form of a narrative summary. Key experimental conditions and results are briefly described for relevant studies. The information in a CHIP is reported as it appears in the published literature; in general, no attempt is made to independently evaluate or validate published data at this stage of assessment. An effort has been made in preparing this volume to have each CHIP conform to a consistent format; however, because these CHIPS were prepared during a three-year period by a variety of authors, a few of the reports do deviate from the format selected.

The OPTS chemical risk assessment process is a sequential one in which chemical problems are evaluated in greater detail at each succeeding stage of the process. In its early stages, limited amounts of information are evaluated on a relatively large number of chemicals; in later stages, more comprehensive information on a relatively few chemicals is assessed. At every stage, the decision is made to evaluate a chemical further or allow it to exit from the process. The decisions that can be made at any given stage are limited by the scope and depth of the data gathering and analysis completed at that stage. Thus, decisions made at the early stages of assessment tend to be more general and tentative than those made at the later stages.

Preparation of a CHIP is part of the first stage in this overall assessment process. The CHIP is OPTS's initial attempt to collect and organize into a report a broad range of information on a chemical of concern. The purpose of a CHIP is to enable OPTS to decide tentatively on an appropriate course of action for the subject chemical. Determination of the need for specific regulatory action is not the immediate goal of the CHIP; rather, it is intended to identify and characterize problems that subsequently may require more thorough investigation and evaluation.

A broad range of possibilities exists regarding the steps taken following the CHIP. Some common alternatives for follow-up action include (1) consideration for more detailed assessment within OPTS; (2) consideration for a testing rule under section 4 of TSCA; (3) acquisition of more information via section 8 of TSCA; (4) referral to other EPA offices or other Government agencies for further consideration and follow-up, as appropriate; and (5) assignment of "low priority" for further assessment by OPTS.

# CHEMICAL HAZARD INFORMATION PROFILE

## Acetonitrile

Date of report: March 9, 1978

This chemical was chosen for study because of its structural similarity to acrylonitrile, a suspected carcinogen.

The following recommendations are made regarding further OTE evaluation of the possible health or environmental hazards of acetonitrile:

(1) Obtain better information on potential for environmental release and human exposure. Available information indicates that significant quantities of acetonitrile may be released to the environment. Use of TSCA Section 8(a) authorities and EPA monitoring of potential release sources should be considered to obtain such information.

(2) Require TSCA Section 8(d) submissions. Information on carcinogenicity and teratogenicity is quite sketchy. Reported teratogenicity studies indicate equivocal results.

(3) Refer acetonitrile to EPA-ORD for mutagenicity testing. No mutagenicity data are currently available.

(4) Update this Chemical Hazard Information Profile (CHIP) based on the additional data found.*

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

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*Subsequent to the review of this CHIP and the selection of the tentative dispositions given above, the TSCA Interagency Testing Committee recommended acetonitrile for primary consideration for possible testing under Section 4(a) of TSCA (44 FR 31866 [June 1, 1979]).

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Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

## Chemical Identity

Acetonitrile ($CH_3$-C=N) is a colorless liquid with an aromatic odor. Its boiling point is 81°C, and its melting point is -41.9°C. Acetonitrile's density is 0.7868 (at 20°C), and its vapor pressure is 100 mm Hg (at 27°C). It has a high polarity, which may contribute to its strong reactivity. Acetonitrile is freely miscible with water, alcohol, ethyl acetate, acetone, ether, chloroform, carbon tetrachloride, and ethylene chloride (ITII, 1976). It is explosive at concentrations of 4.4 to 16.0% by volume in air. Acetonitrile is considered a dangerous disaster hazard since it emits toxic cyanide fumes when heated to decomposition (120°C with alkali). It will react with water, steam, or acids to produce toxic and flammable vapors and can react vigorously with oxidizing materials (Sax, 1968). Synonyms for acetonitrile include methyl cyanide, cyanomethane, and ethanenitrile.

## Production and Use

Acetonitrile can be manufactured by the vapor-phase ammonolysis of glacial acetic acid. The acetonitrile yield is 85-95% after dehydration of the reaction products (Ingwalson, 1971). Another source of acetonitrile is as a byproduct of the propylene-ammonia process for the manufacture of acrylonitrile (Hawley, 1977).

There are only two domestic producers of acetonitrile: E. I. du Pont de Nemours and Co., Inc. (Elastomer Chemicals Department, Beaumont, Tex.) and Standard Oil Co. of Ohio (Vistron Corp., a subsidiary, Chemicals Department, Lima, Ohio) (SRI, 1975). Annual production has been estimated to be 135 x $10^6$ lb (Dorigan et al., 1976).

Acetonitrile is used as a solvent in hydrocarbon extraction processes (especially for butadiene) and as a specialty solvent.* Acetonitrile is the starting material for acetophenone and naphthalene-acetic acid, thiamine, and acetamine.

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*Acetonitrile may be used as a specialty solvent to dissolve cationic textile dyes (Textile World, 1974), to recrystallize steroids, and to remove tars, phenols, and coloring matters from petroleum hydrocarbons (Stecher, 1969).

It is a chemical intermediate in the manufacture of vitamin $B_1$, substituted pyrimidines, and pharmaceuticals. Acetonitrile is used as a solvent in the separation of fatty acids from vegetable oils (Hawley, 1977).

## Health Aspects

The TLV for acetonitrile is 40 ppm (ACGIH, 1971). This is also the time weighted average for worker exposure. Acetonitrile is easily absorbed through mucous membranes because of its high solubility in water. The oral $LD_{50}$ for rats is 3,800 mg/kg. Four-hour rat inhalation studies give an $LC_{50}$ of 8,000 ppm. The $LD_{50}$ for intraperitoneal injections of acetonitrile in mice is 500 mg/kg. $LD_{50}$ for standard application of acetonitrile to rabbit skin is 1,250 mg/kg. The 96-hr aquatic toxicity rating is 1,000 ppm (NIOSH, 1976).

The toxic action of acetonitrile is the same in most animals as it is in man. The compound is metabolized to hydrocyanic acid, which can be found in high levels in the brain, heart, kidney, and spleen (Haguenoer, 1975). Acute symptoms of acetonitrile inhalation include headache, dizziness, increased respiration rate, rapid pulse, vomiting, unconsciousness, and convulsions (coma and death). Chronic symptoms of acetonitrile inhalation include headache, anorexia, dizziness, weakness, and dermatitis (ITII, 1976). Other chronic effects may include growth retardation, metabolic disturbances, and liver enlargement (Dorigan et al., 1976).

Acetonitrile is easily absorbed through mucous membranes because of its high solubility in water. Human inhalation studies on acetonitrile have been conducted. Three subjects were exposed to 40 ppm for 4 hr and two subjects were exposed to 80 and 160 ppm for 4 hr. No adverse reactions were reported at the 40 ppm and 80 ppm inhalation levels. At 160 ppm, one subject noted a slight flushing of the face 2 hr after inhalation and a slight feeling of bronchial tightness 5 hr later. There was no detectable blood cyanide at 40 or 80 ppm. At 160 ppm, there were insignificant changes in blood cyanides. At 40 ppm, one subject exhibited a slightly elevated urinary thiocyanate level. The urinary thiocyanate level changes were insignificant at 40 ppm; they were inconsistent at 80 ppm and not significant at 160 ppm (Pozzani, 1959).

Inhalation of high concentrations of acetonitrile vapors can be fatal. Symptoms are usually delayed 4 to 16 hr and begin with stomach pains and vomiting. Headache, chest pain, asthenia, hypotension, generalized pain, and weakness may follow. The victim may then lapse into coma and convulsions. Death is preceded by a failing of the central nervous system (Desquidt, 1974).

The toxic action of acetonitrile is due to the in vivo metabolism to hydrocyanic acid. Autopsy of one victim revealed densification of the inferior lobes of the lungs and total diffuse necrosis of the brain (Desquidt, 1974). Liquid acetronitrile may also cause skin irritation by direct contact (Stecher, 1969). No references to the mutagenicity of acetonitrile have been found. The reported teratogenic effects of acetonitrile are conflicting. Fetal malformations have been reported in rats from intraperitoneal doses from 0.2 to 1.0 ml/kg (Dorigan et al., 1976). However, other investigators have been unable to produce malformations in fetal pigs (Crowe, 1973). Attempts to produce teratogenic effects in rodents have produced inconsistent results.

## Environmental Aspects

Based on an estimated annual production of 135 x $10^6$ lb of acetonitrile, 69.5 x $10^6$ lb is released to the environment annually (Dorigan et al., 1976). It is unclear whether this release rate accounts for acetonitrile waste from acrylonitrile production. This process may produce and release over 20 x $10^6$ lb per year (Gruber, 1976). In the atmosphere acetonitrile is highly reactive to oxidizing materials. It is infinitely soluble in water (Dorigan et al., 1976) and has been found to be relatively stable in water.* The BOD of 1 mg acetonitrile has been estimated to be 1.4 mg.

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*A concentration of approximately 2.4 mg/l can be maintained in reservoir water for 4 days (Rubinskii, 1969).

## REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). Documentation of TLV's. Cincinnati, Ohio. 1971.

Crowe, M. W. Teratogenic capability of tobacco (Nicotiana tobacum) and those chemicals commonly applied to the growing plant. Tob. Health Workshop Conf. Proc. 42:98-202, 1973.

Desquidt, J. et al. Poisonings by acetonitrile. A fatal case. Eur. J. Toxicol. 7(2):91-97, 1974.

Dorigan, J. et al. Scoring of Organic Air Pollutants. MITRE Corp. (for EPA). 1976.

Gruber, G. I. Assessment of Industrial Hazardous Waste Practices, Organic Chemicals, Pesticides and Explosives Industries. Redondo Beach, Calif., TRW (for EPA). 1976.

Haguenoer, J. M. et al. Experimental acetonitrile intoxication: Acute intoxication by an intraperitoneal route. Eur. J. Toxicol. 8(2):94-101, 1975.

Hawley, G. G. (ed.). Condensed Chemical Dictionary, 9th ed. New York, Van Nostrand Reinhold Co. 1977.

Ingwalson, R. W. Nitriles. In Kirk-Othmer Encyclopedia of Chemical Technology, Supplement. 1971.

ITII (International Technical Information Institute). Toxic and Hazardous Industrial Chemicals Safety Manual. Tokyo. 1976.

NIOSH. Registry of Toxic Effects of Chemical Substances, 1976 ed.

Pozzani, U. C. et al. An investigation of the mammalian toxicity of acetonitrile. J. Occup. Med. 1:634, 1959.

Rubinskii, N. D. Effect of acetonitrile and succinonitrile on the sanitary conditions of reservoirs. Gig. Naselennykj Mest 8:20-24, 1969. (From Chem. Abstr. 73:91026j)

Sax, N. I. Dangerous Properties of Industrial Materials, 3rd ed. New York, Van Nostrand Reinhold Co. 1968.

SRI (Stanford Research Institute). Directory of Chemical Producers. Menlo Park, Calif. 1975.

Stecher, P. G. (ed.). The Merck Index. Rahway, N.J., Merck and Co., Inc. 1969.

## ADDENDUM

It has been found that a standardized (Crowe, 1976) second puff of cigarette smoke contains 0.31 mg acetonitrile. A smoker may adsorb between 73 and 82% of this, depending on past smoking habits.

## Reference

Dalman, T. et al. Mouth adsorption of various compounds in cigarette smoke. Arch. Environ. Health 16(6): 831-835, 1968.

# CHEMICAL HAZARD INFORMATION PROFILE

## Acrolein

Date of report: March 10, 1978

This chemical was chosen for study because of its reported presence in air and water samples.

Acrolein is not recommended for further priority evaluation within OTS at this time. Available information indicates that most human exposure to acrolein is confined to the workplace. There is an existing OSHA standard for acrolein. Significant environmental exposure is unlikely because of acrolein's high reactivity and apparently low release rate.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

## Chemical Identity

Acrolein (2-propenal, acrylaldehyde, or allyl aldehyde) is a colorless to yellowish liquid. It has a highly disagreeable, choking odor and is flammable. Acrolein is soluble in water, alcohol, and ether. It has a boiling point of 52.7°C. Upon exposure to light and air, acrolein polymerizes to form disacryl, an inactive, gelatinous substance (Hawley, 1971).

## Production and Use

Acrolein is currently produced only by Shell Chemical Co., Norco, La., and Union Carbide Corp., Chemicals and Plastics Division, Taft, La. (SRI, 1977). The only method used to manufacture acrolein is the catalytic vapor-phase oxidation of propylene (School, 1973). U.S. production of isolated acrolein in 1974 is estimated to have been 61 million lb. An additional 100-150 million lb was produced and consumed captively for production of acrylic acid and esters (U.S. EPA, 1977b).

The U.S. consumption pattern of isolated acrolein in 1974 was estimated as follows: glycerin, 50%; synthetic methionine, 25%; other applications, 25%. "Other applications" include: manufacture of 1,2,6-hexanetriol, glutaraldehyde, glyceraldehyde, perfume, colloidal forms of metals, and numerous other organic compounds; as an aquatic herbicide, molluscicide, slimicide, and algicide; and in etherification of food starch (U.S. EPA, 1977b).

## Health Aspects

### General Toxicity

Acrolein is a severe irritant to the eyes and respiratory tract. Yant et al. (1930) reported that 1 ppm caused "practically intolerable eye irritation with lacrimation" within 5 min of exposure. The rat inhalational $LC_{50}$ is 0.75 mg/l for 10-min exposure (Champeix and Catilina, 1975). Rat oral $LD_{50}$ is 46 mg/kg, and human $LC_{LO}$ is 153 ppm/10 min (NIOSH, 1975).

Rats continuously exposed to 0.55 ppm acrolein for 11 to 21 days had significantly lower body weight, liver weight, and serum acid phosphatase levels than controls. They also showed signs of upper respiratory tract irritation, significant lowering of alveolar macrophage number, and high susceptibility to *Salmonella enteritidis* infection (Bouley et al., 1976).

Continuous 90-day exposure at 0.22 ppm caused inflammation in liver, lung, kidney, and heart of monkeys, guinea pigs, and dogs. Exposure to 1.8 ppm caused squamous cell metaplasia and basal cell hyperplasia of the trachea in monkeys (Lyon et al., 1970).

### Carcinogenicity

In a study with hamsters, Peron and Kruysse (1971) found no tumors attributable to acrolein exposure (4.0 ppm, 7 hr/day, 5 days/week, 52 weeks). Acrolein exposure did not increase the number of tumors in animals treated with both acrolein and either benzo(a)pyrene or diethylnitrosamine.

### Mutagenicity

Acrolein has been found to be mutagenic in the yeast *S. cerevisiae* (Izard, 1973), the alga *D. bioculata* (Izard, 1967), and the fruit fly *D. melanogaster* (Rapoport, 1948).

Negative results have been found in the bacteria *E. coli* (Ellenberger and Mohn, 1976) and *S. typhimurium* (Anderson et al., 1972) and in the mouse dominant lethal test (Epstein et al., 1972).

## Hygienic Standards

U.S. Occupational Health Standard - air: TWA, 0.1 ppm.

American Conference of Government Industrial Hygienists: TLV, 0.1 ppm.

## Environmental Aspects

The total release rate of acrolein into the environment is not known. Besides fugitive emissions from industrial processes, acrolein is formed in the environment by burning tobacco and by heating fats or glycerine (Plotnikova, 1957).

In water, oxidation of acrolein by RO radical may be fairly rapid (U.S. EPA, 1977a). Biodegradation in water also appears rapid, as the 10-day BOD is 33% of the theoretical value (Dorigan et al., 1976). In air, aldehydes are expected to photodissociate to RCO and H atoms rapidly and competitively with their oxidation by HO radical, for a half-life of 2 to 3 hr (Calvert and Pitts, 1966; Hendry, 1977).

The 24-hr and 48-hr $LC_{50}$ values to harlequin fish are, respectively, 0.14 and 0.06 ppm (Alabaster, 1969). Exposure to 1.0 ppm totally inhibited multiplication of the marine alga D. bioculata (Champeix and Catalina, 1975). Acrolein has demonstrated ciliastatic effects in mammals (Guillerm et al., 1961), molluscs (Wynder et al., 1965), and algae (Izard and Testa, 1968).

## REFERENCES

Alabaster, J. S. Survival of fish in 164 herbicides, insecticides, fungicides, wetting agents and miscellaneous substances. Int. Pest. Contr. 11(2): 29-35, 1969.

Anderson, K. J., E. G. Leighty, and M. T. Takahashi. Evaluation of herbicides for possible mutagenic properties. J. Agr. Food Chem. 20(3):649-656, 1972.

Bouley, G., A. Dubreuil, J. Godin, M. Boisset, and C. Boudene. Phenomena of adaptation in rats continuously exposed to low concentrations of acrolein. Ann. Occup. Hyg. 19(1):27-32, 1976.

Calvert, J. G., and J. N. Pitts. Photochemistry. New York, John Wiley and Sons. 1966. (As cited by U.S. EPA, 1977a)

Champeix, J., and P. Catilina. Les Intoxications par l'Acroleine. Masson, Paris, 1975. (As cited by Izard and Libermann, Mutat. Res. 47:133, 1978)

Dorigan, J., B. Fuller, and R. Duffy. Scoring of Organic Air Pollutants. Chemistry, Production and Toxicity of Selected Synthetic Organic Chemicals. MITRE Corp. 1976.*

Ellenberger, J., and G. R. Mohn. Comparative mutagenicity of cyclophosphamide and some of its metabolites. Mutat. Res. 38:120-121, 1976. (As cited by Izard and Libermann, Mutat. Res. 47:125, 1976)

Epstein, S. S., E. Arnold, J. Andrea, W. Bass, and Y. Bishop. Detection of chemical mutagens by the dominant lethal assay in the mouse. Toxicol. Appl. Pharmacol. 23:288-325, 1972. (As cited by Izard and Libermann, Mutat. Res. 47:132, 1978)

Guillerm, R., R. Dadre, and B. Vignon. Effects inhibiteurs de la fumee de tabac sur l'activite ciliavie de l' epithelium respirative, et natures des composants responsables. C. R. Acad. Nat. Med. 145:416-425, 1961. (As cited by Izard and Libermann, Mutat. Res. 47:123, 1978)

Hawley, G. G. (ed.). The Condensed Chemical Dictionary, 8th ed. New York, Van Nostrand Reinhold Co. 1971.

Hendry, D. G. Private communication, 1977. (As cited by U.S. EPA, 1977a)

Izard, C. Sur la multiplication de Dunaliella bioculata en presence de la phase gayeuse de fumee de cigarette et sur l'obtention de mutations en presence d' acroleine. C. R. Acad. Sci. Ser. D 265:1799-1802, 1967. (As cited by Izard and Libermann, Mutat. Res. 47:128, 1978)

Izard, C. Recherches sur les effects mutagenes de l' acrolein et de ses deux epoxydes: le glycidol et le glycidal, sur Saccharomyces cerevisiae. C.R. Acad. Sci. Ser. D 276: 3037-3040, 1973. (As cited by Izard and Libermann, Mutat. Res. 47:126, 1978)

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*This document was prepared for the U.S. Environmental Protection Agency by the MITRE Corp. It is a secondary source and does not cite its primary references. Thus, verification of some information is not possible. The environmental release data were taken from the NSF/Rann Research Program on Hazard Priority Ranking of Manufactured Chemicals.

Izard, C., and P. Testa. Recherches sur les effects de la fumee de la cigarette et de certains constituants sur la motilitie et la multiplication du Dunaliella bioculata. Ann. Dir. Equip. Exploit. Ind. Tab. Alumettes, Sec. 1, No. 6, p. 121-156, 1968. (As cited by Izard and Libermann, Mutat. Res. 47:124, 1978)

Lyon, J. P., T. J. Jenkins, Jr., R. A. Jones, R. A. Coon, and J. Siegel. Repeated and continuous exposure of laboratory animals to acrolein. Toxicol. Appl. Pharmacol. 17(3): 726-732, 1970.

NIOSH. Registry of Toxic Effects of Chemical Substances. 1975.

Peron, V. J., and A. Kruysse. Effects of exposure to acrolein vapor in hamsters simultaneously treated with benzo(a)-pyrene or diethylnitrosamine. J. Toxicol. Environ. Health 3:379-394, 1971.

Plotnikova, M. M. Acrolein as an atmospheric air pollutant. Gig. Sanit. 22(6):1015, 1957. From B. S. Levine (ed.), U.S.S.R. Literature on Air Pollution and Related Occupational Diseases, vol. 3, 1960, p. 188-194.

Rapoport, I. A. Mutatsii pod vlianiem mepredel' nyh al' degidov. Dokl. Akad. Nauk SSSR 61:713-715, 1948. (As cited by Izard and Libermann, Mutat. Res. 47:131, 1978)

SRI (Stanford Research Institute). Directory of Chemical Producers. Menlo Park, Calif. 1977.

School, G. E. Make acrolein from propylene. Hydrocarbon Process., Sept. 1973, p. 218-220.

U.S. EPA. Review of the Environmental Fate of Selected Chemicals Task 3. EPA 560/5-77-003, PB 267121/AS. 1977a. p. 52.

U.S. EPA. A Study of Industrial Data on Candidate Chemicals for Testing. EPA 560/5-77-006. 1977b. p. 487, 488.

Wynder, E. L., D. A. Goodman, and D. Hoffman. Ciliatoxic components in cigarette smoke, II. Carboxylic acids and aldehydes. Cancer 18:505-509, 1965. (As cited by Izard and Libermann, Mutat. Res. 47:123, 1978)

Yant, W. B., H. Schrenk, P. Patty, and R. Sayers. Acrolein as a warning agent for detecting leakage of methyl chloride from refrigerators. U.S. Bureau of Mines Report of Investigation No. 3027. (As cited by Kane and Alarie, Sensory irritation to formaldehyde and acrolein during single and repeated exposures in mice, American Ind. Hyg. Assoc. J., vol. 38, 1971)

# CHEMICAL HAZARD INFORMATION PROFILE

## Adipate Ester Plasticizers

Date of report: January 5, 1978

This category of chemicals was chosen for study after incidents of respiratory ailments ("meat-wrappers syndrome") were reported in workers exposed to food wraps which contain adipate ester plasticizers. Although no information supporting these claims was found in the course of preparing this document, information was found which indicates a potential for mutagenic and teratogenic effects.

Phase I assessment is recommended for the adipates. Relatively little information was found concerning either the amount of adipate esters released into the environment or the environmental fate of these chemicals. This lack of information, coupled with the fact that adipate esters are produced in fairly high volume, suggests that environmental monitoring may be needed to allow better estimation of the extent of nonoccupational exposure to adipate esters. Monitoring data obtained by SAD will be forwarded to CREB for use in the Phase I assessment.

It is also recommended that CHIB perform a chemical technology review of diacid plasticizers.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

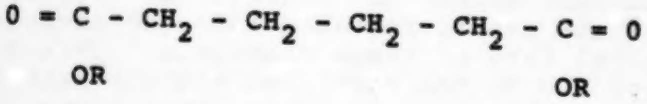
Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

## Chemical Identity

Adipate ester plasticizers are nonvolatile oily liquids or low-melting solids. They are generally used to improve the low-temperature flexibility of polyvinyl chloride (PVC) compounds (CCD, 1977).

A plasticizer is an organic compound added to a high-molecular-weight polymer both to facilitate processing and to increase the flexibility and toughness of the final product by internal modifications (solvation) of the polymer molecule. The polymeric structure is initially held together by secondary valence bonds; the plasticizer replaces some of these with plasticizer-to-polymer bonds, thus aiding movement of the polymer chain sections. Plasticizers are classified as primary (high compatibility) and secondary (limited compatibility).

The most widely used adipate ester plasticizer is di(2-ethylhexyl) adipate, which accounts for about two-thirds of the adipate ester plasticizer market. The other large-volume component of this market is n-octyl n-decyl adipate, representing approximately 13% of the total. The balance is divided among a number of adipic acid esters including diisodecyl adipate, diisooctyl adipate, n-hexyl n-decyl adipate, di(2-butoxyethoxy)ethyl adipate, and others (CEH, 1976).



$$O = \underset{OR}{C} - CH_2 - CH_2 - CH_2 - CH_2 - \underset{OR}{C} = O$$

General formula for adipic acid esters

## Production and Use

Most plasticizers are products of simple esterification reactions, which can be readily carried out in heated kettles with agitation and provisions for water take-off. Nevertheless, while some plants produce plasticizers by such batch methods, other, newer plants operate continuously and in a highly automated fashion. Esterification catalysts such as sulfuric acid or p-toluenesulfonic acid speed the reaction and are later removed in a washing step. The purity requirements for commercial plasticizers are very high; adipate esters are usually almost colorless and have little odor (CEH, 1976).

Adipic acid esters are prepared via the reaction of adipic anhydride with an aliphatic alcohol to yield the desired product (CEH, 1976).

The production of adipate esters has increased appreciably in recent years. The major producers of adipate plasticizers are Hatco, Monsanto, Rohm and Haas, Tennessee Eastman, and U.S.S. Chemicals. Only Monsanto is a major producer of adipic acid and is also believed to be the largest producer of the most popular adipate plasticizer, di(2-ethylhexyl) adipate. See Table 1 for annual domestic production figures. Table 2 presents the 1971 production figures for the major adipate plasticizers. Along with the major adipate plasticizers are a number of apparently small-volume adipate plasticizers used in specialty applications. Table 3 lists all the adipate plasticizers identified in the Modern Plastics Encyclopedia (1975). Despite the significant production volume of the adipate plasticizers, as a class they represent only a small fraction of the total plasticizer market. As can be seen in Table 4, adipates represent less than 5% of a market dominated by phthalate esters.

Table 1. Annual Domestic Production of Adipate Plasticizers (millions of lbs)

| Year | Di(2-ethylhexyl) adipate | Others[a] | Total |
|---|---|---|---|
| 1955 | 2.7 | 7.9 | 10.6 |
| 1960 | 3.0 | 14.3 | 17.3 |
| 1965 | 14.7 | 33.1 | 47.8 |
| 1970 | 35.0 | 19.0 | 54.0 |
| 1974 | 40.6 | 23.5 | 64.1 |

Source: CEH, 1976.

[a] Includes primarily n-octyl n-decyl adipate and the following: diisodecyl adipate; diisooctyl adipate; n-hexyl n-decyl adipate; and di(2-butoxyethoxy)ethyl adipate.

Table 2. Adipate Ester Production, 1971

| Type | % |
|---|---|
| Di(2-ethylhexyl) adipate (DOA) | 55 |
| Dioctyl adipate | 14 |
| n-Octyl n-decyl adipate | 13 |
| Diisodecyl adipate | 6 |
| n-Hexyl n-decyl adipate | 5 |
| Di(2-butoxyethoxy)ethyl adipate | 3 |

Source: CEH, 1976.

Table 3. Commercial Adipate Ester Plasticizers[a]

| Name | No. of manufacturers and importers |
|---|---|
| Dimethyl adipate | 7 |
| Dibutyl adipate | 2 |
| Diisobutyl adipate | 3 |
| Di(2-ethylhexyl) adipate (DOA) | 16 |
| Dinonyl adipate | 2 |
| n-Octyl n-decyl adipate | 4 |
| Diisodecyl adipate | 9 |
| Polypropylene adipate | 1 |

Source: U.S. EPA (1979).*

[a] This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

Table 4. U.S. Production and Plasticizers by Major Type, 1974

| Type | % |
|---|---|
| Phthalate esters | 71.8 |
| Epoxy esters | 8.8 |
| Phosphate esters | .3 |
| Adipate esters | 3.8 |
| Polymeric plasticizers | 3.0 |
| Other aliphatic esters | 1.1 |
| Other plasticizers | 4.2 |

Source: CEH, 1976.

Over 85% of all aliphatic adipate ester plasticizers are used to impart low-temperature flexibility to polyvinyl chloride (PVC) formulations (see Table 5). Adipates represent the predominant category of aliphatic plasticizers; azelates and sebacates are small-volume speciality aliphatic plasticizers. In recent years, with the increased availability of cheaper linear phthalates, the total consumption of aliphatic plasticizers has remained virtually static.

In addition to PVC applications, adipate plasticizers are used to a much lesser extent with natural and synthetic rubbers, polystyrene, and cellulose derivatives (e.g., nitrocellulose lacquers). These plasticizers are characterized by low initial viscosity stability for plastisol

Table 5. Domestic Aliphatic Plasticizer[a] Consumption, 1974 (%)

| Application | Consumption |
|---|---|
| Use with polymers | |
| PVC resins | 76 |
| Other vinyl resins | |
| Cellulose ester plastics | 3 |
| Synthetic elastomers | |
| Other polymers | |
| Other uses | 21 |
| Total | 100 |

Source: CEH, 1976.

[a] Includes adipates (predominantly), sebacates, and azelates.

formulations, excellent clarity for sheeting and film, good electrical resistivity, and low volatility for high-temperature applications such as wire covering and insulation.

In PVC plasticizers, adipate diesters [chiefly di(2-ethylhexyl) adipate] are used to impart low-temperature flexibility and resilience when, and to the extent, needed. Examples of PVC plastics containing discrete amounts of adipate plasticizers include coated fabrics for automobile seating, film for produce and meat packaging, insulation of certain types of electrical and communication wires, and others. Adipate plasticizers were among the first plasticizers approved by FDA for use in food storage and preparation areas, where they have found increasing popularity (e.g., coating for refrigerator shelves and kitchen appliances). The major application of adipate plasticizers in this field is in food wraps and packaging, and this market is expanding rapidly (CEH, 1976).

One of the chief concerns involved in the selection of the correct adipate plasticizer is the compatibility each has for the particular resin. Adipic acid esters of linear alcohols, chiefly in the n-octyl to n-decyl range, for example, have found increasing use because their effectiveness in imparting low-temperature flexibility is somewhat greater than that of esters of branched alcohols; in addition, they are also much less volatile. On the other hand, their compatibility and fusion characteristics are inferior to those of di(2-ethylhexyl) adipate (CEH, 1976). Refer to Table 6 for a summary of compatibility qualities of several adipate plasticizers.

Table 6. Adipate Plasticizer Compatibility with Various Plastics[a]

| Plasticizer | CA | CAB | CN | EC | PM | PS | VA | VB | PVC |
|---|---|---|---|---|---|---|---|---|---|
| Diisobutyl adipate | U | C | C | U | U | U | C | U | C |
| DOA | P | C | C | C | P | C | P | P | C |
| Diisodecyl adipate | P | C | C | C | P | P | P | P | C |
| Di(2-butoxyethyl) adipate | P | C | C | C | C | C | P | C | C |

Source: Adapted from: Darby and Sears, 1968.

[a] Resins used: CA, cellulose acetate; CAB, cellulose acetate-butyrate; CN, cellulose nitrate; EC, ethylcellulose; PM, polymethyl methacrylate; PS, polystyrene; VA, polyvinyl acetate; VB, polyvinyl butyryl; PVC, polyvinyl chloride. Code for compatibility: C, compatible; P, partially compatible; U, unknown.

## Health Aspects

### Dominant Lethal Mutations and Antifertility Effects

Male mice of demonstrated fertility were injected IP with a single dose of 0.5, 1.0, 5.0, or 10.0 ml/kg of di(2-ethylhexyl) adipate (DOA) or a single injection of 0.44, 0.73, 1.10, or 1.46 ml/kg of diethyl adipate (DEA). Ten males were injected at each dose level and allowed to mate with two virgin females per week for 8 weeks. Both DOA and DEA produced dose-related antifertility and mutagenic effects, as indicated by a reduced percentage of pregnancies and an increased number of early fetal deaths. The highest dose of DOA and the two largest doses of DEA yielded a distinct reduction in the incidence of pregnancies, especially during the first 3- to 4-week period postinjection. This antifertility effect was less evident with the lower dose levels. There also occurred a reduction in the number of implantations and live fetuses per pregnancy for one or more of the higher dose levels of both DOA and DEA. Mutagenic effects, as expressed by an increase in the number of early fetal deaths, displayed a significant degree of dose dependence, with the higher doses yielding more early fetal deaths than the lower doses. These dominant lethal mutations were observed for both adipates during the 3-week period immediately following injection. However, DOA also induced dominant lethal effects during the period 4-8 weeks postinjection. This indicates that DOA produced dominant lethal mutations in both the postmeiotic and premeiotic stages of spermatogenesis in mice (Singh et al., 1975).

## Embryotoxic and Teratogenic Effects

Seven adipates were evaluated for their embryonic-fetal toxicity and teratogenic effects in rats. The tested adipates included dimethyl, diethyl (DEA), dipropyl, diisobutyl, di-n-butyl, di(2-ethylhexyl) (DOA), and dicyclohexyl adipate. The adipates were tested in female rats by the IP injection of varying doses on the 5th, 10th, and 12th days of gestation (see Table 7).

Table 7. Embryonic-Fetal Toxicity of Adipate Esters on Rat Fetuses

| Adipate ester | Injection vol (ml/kg) | Resorptions (%) | Abnormalities Gross | Abnormalities Skeletal | Abnormalities Visceral |
|---|---|---|---|---|---|
| Dimethyl | 0.0603 | 6.8 | 0 | 0 | 0 |
| | 0.1809 | 14.1 | 1.8 | 7.4 | 0 |
| | 0.3617 | 1.8 | 3.6 | 13.8 | 0 |
| | 0.6028 | 5.7 | 8.0 | 19.2 | 0 |
| Diethyl (DEA) | 0.0837 | 1.9 | 0 | 0 | 8.3 |
| | 0.2512 | 7.0 | 1.9 | 0 | 0 |
| | 0.5024 | 9.3 | 2.0 | 4.0 | 4.0 |
| | 0.8373 | 10.7 | 4.2 | 8.0 | 0 |
| Dipropyl | 0.1262 | 3.2 | 0 | 0 | 0 |
| | 0.3786 | 10.9 | 2.0 | 0 | 0 |
| | 0.7572 | 9.8 | 3.6 | 0 | 0 |
| | 1.2619 | 20.0 | 5.6 | 5.3 | 0 |
| Diisobutyl | 0.1983 | 3.6 | 0 | 0 | 0 |
| | 0.5950 | 1.6 | 3.2 | 6.3 | 0 |
| | 1.1900 | 4.8 | 1.7 | 10.0 | 0 |
| | 1.9833 | 3.2 | 8.3 | 9.7 | 3.4 |
| Di-n-butyl | 0.1748 | 3.8 | 0 | 0 | 0 |
| | 0.5244 | 4.9 | 1.7 | 0 | 3.7 |
| | 1.0488 | 2.9 | 3.0 | 0 | 0 |
| | 1.7480 | 9.4 | 5.4 | 6.7 | 3.8 |
| Di(2-ethylhexyl) (DOA) | 1.00 | 5.3 | 0 | 3.6 | 0 |
| | 5.00 | 3.1 | 1.6 | 3.4 | 3.2 |
| | 10.00 | 7.0 | 3.8 | 7.1 | 4.0 |
| Dicyclohexyl | 0.1700 | 14.5 | 0 | 0 | 0 |
| | 0.5100 | 19.6 | 10.0 | 0 | 0 |
| | 1.0201 | 19.4 | 6.3 | 3.8 | 0 |
| | 1.7002 | 20.0 | 8.5 | 4.0 | 0 |

Source: Adapted from Singh et al., 1973.

The administered doses were based on the acute toxicity of each compound as follows: 1/30, 1/10, 1/5, and 1/3 of the acute $LD_{50}$ for each substance (except DOA, which had little apparent acute toxicity). The rats were sacrificed on the 20th day of gestation (1 day before expected parturition) and examined for gross, skeletal, and visceral abnormalities.

All of the adipates were found to exert some degree of damage upon the developing embryo and fetus:

(1) Dicyclohexyl adipate caused a significant increase in resorptions at all four dose levels, indicating an early embryotoxic effect. In addition, dead fetuses were found at all dose levels, indicative of a later toxic action as well. A number of gross abnormalities were noted at the three higher doses; most abnormalities took the form of hemangiomas of various parts of the body, although twisted hindlegs were often also observed. Skeletal abnormalities were seen in a few mice at the two highest dose levels, while no visceral changes were seen in any of the groups.

(2) Dimethyl adipate also displayed a considerable degree of embryotoxicity and teratogenicity. In the highest dose group, several fetuses had hemangiomas, 5 of 26 examined fetuses had skeletal abnormalities, 1 fetus lacked a left kidney, and 1 had an angulated anal opening. In the second highest dose group, 1 fetus did not have a tail and 4 of 29 examined had skeletal abnormalities. The next lower dose level produced several abnormal fetuses, albeit at a lower frequency, with changes similar to those seen at the two higher levels. The lowest dosage did not produce any noted abnormalities.

(3) Diisobutyl adipate produced a number of abnormal changes in the offspring of treated rats. At the highest level, hemangiomas were noted in several fetuses, as were twisted hindlegs and other skeletal malformations. The next lower dose groups yielded fetuses with hemangiomas and skeletal malformations but no examples of twisted hindlegs. No abnormalities were seen in the lowest group.

(4) Diethyl, dipropyl, di-n-butyl, and di(2-ethylhexyl) adipate produced few gross, skeletal, or visceral abnormalities; these occurred predominantly at the higher dose levels.

The study concluded that, while all of the tested adipates exerted some deleterious effects on the developing embryo and fetus, the degree of injury was significantly less than that seen with similar doses of phthalate ester analogs (Singh et al., 1973).

Acute Toxicity

The adipate esters are characterized by a low to moderate degree of acute toxicity. Table 8 presents a summary of the results from several acute toxicity studies.

Table 8. Summary of Adipate Ester Acute Toxicity Studies

| Adipate ester | Oral $LD_{50}$ (g/kg) | IP $LD_{50}$ (ml/kg) | Species |
|---|---|---|---|
| Dimethyl | | 1.8[a] | Rat |
| Diethyl | 1.6[b] | 2.5[a] | Rat |
| | | 2.2[c] | Mouse |
| Dipropyl | | 3.8[a] | Rat |
| Di-n-butyl | 12.9[d] | 5.2[a] | Rat |
| Diisobutyl | | 6.0[a] | Rat |
| Dicyclohexyl | | 5.1[a] | Rat |
| Di(2-ethylbutyl) | 5.6[e] | | Rat |
| Di(2-ethylhexyl) | 9.1[d] | 50.0[a] | Rat |
| (DOA) | 20-50[b] | | Rat |
| | | 100.0[c] | Mouse |
| Di(2-hexyloxyethyl) | 4.3[e] | | Rat |
| Di[2-(2-ethylbutoxy)]ethyl | 3.3[e] | | Rat |
| Didecyl | 25.0[b] | | Rat |
| | 12.8-25.8[b] | | Mouse |

[a] Singh et al., 1973.
[b] Fassett, 1963.
[c] Singh et al., 1975.
[d] Smyth et al., 1951.
[e] Smyth et al., 1954.

Gaunt et al. (1969) tested the acute toxicity of dialkyl 79 adipate (ester of adipic acid and a mixture of alcohols with 7-9 carbon atoms) in rats and mice. The oral $LD_{50}$ in mice was between 8 and 12 g/kg; 20 g/kg administered orally to rats produced diarrhea as the only symptom. (Dialkyl 79 adipate is used as a plasticizer for PVC.)

## Subacute Toxicity

The subacute toxicity of di(2-ethylhexyl) adipate has been tested by several investigators. Fassett (1963) reported a study in which rats were fed diets containing 0.5, 2.0, or 5.0% DOA (approximately 250, 1,000, or 2,500 mg/kg/day for about a month) and were without effect except for growth retardation at the 5% level. The same study found only a transient loss of appetite in dogs fed 2 g/kg/day of DOA for 2 months.

Smyth et al. (1951) fed DOA to rats at doses ranging from 0.16-4.74 g/kg/day for 30 days. The investigators found altered organ weights and a reduction in appetite and growth in rats receiving 2.92 g/kg daily. Doses of 4.74 g/kg were subacutely lethal, while 9.11 g/kg was acutely fatal. The no-effect dose was 0.6 g/kg.

Dialkyl 79 adipate was fed to rats at 0.0, 0.125, 0.25, 0.5, or 1.0% of the diet (approximately 0, 63, 125, 250, or 500 mg/kg/day) for 98 days. No effects were seen at or below 0.25% of the diet. At the 1.0% level, weight gain was lower in females, the relative kidney weight increased in both sexes, and the hemoglobin concentration was reduced, also in both sexes. In the 0.5% group, females displayed an increase in relative kidney weight (Gaunt et al., 1969).

## Environmental Aspects

MITRE Corp. (1976) estimates that 39.4 million lb of di(2-ethylhexyl) adipate was released to the environment in 1972.

Di(2-ethylhexyl) adipate has been identified at a concentration of 30 ppb in the Monatiquot River in Massachusetts. This is apparently the first time that an adipate plasticizer has been identified in water and indicates that plasticizers in addition to phthalates (which are recognized widespread environmental contaminants) are entering the aqueous environment (Hites, 1973).

The biodegradability of three adipate esters was determined in acclimated, activated sludge systems. Rapid primary degradation (67-99+%) was observed at 3 and 13 mg/l feed levels for di(2-ethylhexyl) adipate, di-n-hexyl adipate, and hexyl nonyl adipate over a 24-hr period (Saeger et al., 1976).

The phytotoxic effects of gases emitted by PVC plastic covering materials were tested on various vegetable crops. Among 25 plasticizers tested, diisobutyl phthalate and di(2-

ethylhexyl) adipate were the most injurious to vegetable plants. These plasticizers were apparently volatilized to a phytotoxic degree from the plastic sheets under "normal" conditions (Inden and Tachibana, 1975).

Several studies (Rubin, 1973; Easterling et al., 1974) have demonstrated the migration of di(2-ethylhexyl) adipate from plastic biomedical devices into blood. Up to 4 mg of DOA was extracted from "medical grade" PVC tubing by human plasma circulated for 6 hr at 37°C. DOA was also found in blood stored in plastic packs.

## REFERENCES

CEH (Chemical Economics Handbook). Menlo Park, Calif., Stanford Research Institute. 1976.

CCD (Chemical Dictionary). 9th ed. New York, Van Nostrand Reinhold Co. 1977.

Darby, J. R., and J. K. Sears. Plasticizers. In Kirk-Othmer Encyclopedia of Chemical Technology, vol. 15. New York, Interscience Publishers. 1968. p. 720.

Easterling, Ronald E. et al. Plasma extraction of plasticizers from "medical grade" polyvinylchloride tubing (38389). Proc. Soc. Exp. Biol. Med. 147:572, 1974.

Fassett, David W. Esters. In Frank A. Patty (ed.), Industrial Hygiene and Toxicology, vol. II. New York, Interscience Publishers. 1963. p. 1890.

Gaunt, I. F. et al. Acute (rat and mouse) and short-term (rat) toxicity studies on dialkyl 79 adipate. Food Cosmet. Toxicol. 7:35, 1969.

Hites, R. A. Analysis of trace organic compounds in New England rivers. J. Chromatogr. Sci. 11(11):570, 1973.

Inden, T., and S. Tachibana. Damage on crops by gases emitted from the plastic materials for covering. Mie Daigaku Mogakuba Gakujutsu Hokoku. 50:1, 1975. (Summary)

MITRE Corp. Scoring of Organic Air Pollutants: Chemistry, Production, and Toxicity of Selected Synthetic Organic Chemicals. September 1976.

Modern Plastics Encyclopedia, 52(10A). New York, McGraw-Hill. 1975.

Rubin, R. J. Biomedical implications of the migration of phthalate ester plasticizers from PVC plastic. Tech. Pap., Reg. Tech. Conf. Soc. Plast., March 20-22, 1973, 81. (Abstract)

Saeger, V. W. et al. Activated sludge degradation of adipic acid esters. Appl. Environ. Microbiol. 31(5):746, 1976.

Singh, A. R. et al. Embryonic-fetal toxicity and teratogenic effects of adipic acid esters in rats. J. Pharm. Sci. 62(10):1596, 1973.

Singh, A. R. et al. Dominant lethal mutations and antifertility effects of di-2-ethylhexyl adipate and diethyl adipate in male mice. Toxicol. Appl. Pharmacol. 32:566, 1975.

Smyth, Henry F. et al. Range-finding toxicity data: List IV. Arch. Ind. Hyg. 4:119, 1951.

Smyth, Henry R. et al. Range-finding toxicity data: List V. Arch. Ind. Hyg. 10:61, 1954.

U.S. EPA. Toxic Substances Control Act Chemical Substance Inventory, Office of Pesticides and Toxic Substances, Washington, D. C.

# CHEMICAL HAZARD INFORMATION PROFILE

## Aluminum and Aluminum Compounds

Date of report: September 1, 1976

This group of compounds was chosen for study because of its high production volume and high exposure potential.

Aluminum is not recommended for further priority evaluation within OTS at this time. None of the available information indicates that aluminum may present a hazard to humans or to the environment.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

## Chemical Identity

Aluminum is the most abundant metal and third most abundant element, making up 7.5% of the earth's crust. The atomic number of aluminum is 13 and the atomic weight is 26.98. The melting point is 660°C and the boiling point is 2,327°C. Aluminum's density is 2.7 g/ml. Aluminum is an excellent thermal and electrical conductor and is highly resistant to most corrosive agents, aided by the formation of a thin protective film of oxide on exposure to the moisture in air. In its pure form, aluminum is a silvery white metal with the highest reflectivity of any metal in the visible and ultraviolet spectra. Pure aluminum is very malleable and ductile, and many alloys with copper, zinc, silicon, manganese, and magnesium are produced for various commercial applications.

Aluminum does not exist naturally in the elemental form, but is a constituent of many minerals, both rare and abundant. Aluminum oxide, $Al_2O_3$, exists naturally in many forms, including the precious stones sapphire, ruby, and emerald and the minerals bayerite, bohemite, diaspore, gibbsite, and corundum. The minerals differ primarily in their degree of hydration and crystal structure, and are often grouped under the collective term bauxite. They are water insoluble and increase in density from 2.4 to 4.0 g/ml as the water content decreases from the trihydrate to the anhydrous form. Corundum, the natural form of anhydrous aluminum oxide, has a hardness of 9 on the Mohs scale as compared with 1 for graphite and 10 for diamond, and finds widespread applications as an abrasive. Other naturally occurring aluminum minerals include albite, $NaAlSi_3O_8$; amonthite, $CaAl_2Si_2O_8$; biotite and muscovite, complex micas; cryolite, $Na_3AlF_6$; kaolinite, $Al_4Si_4O_{10}(OH)_8$; orthoclase, $KAlSi_3O_8$; and spinel, $MgAl_2O_4$.

Most inorganic aluminum compounds are white or colorless crystals that are sparingly soluble in water and insoluble in ethanol. The organic salts tend to be yellowish solids that are readily soluble in water and organic solvents. Aluminum halides and hydrides are violently reactive with water and generally soluble in nonpolar organic solvents. Most aluminum salts possess astringent and antiseptic properties.

Organoaluminum compounds are highly reactive liquids. Those in the lower alkyl series are spontaneously flammable in air unless diluted to 25% or less with organic solvents. All types are highly pyrophoric and will react with any source of active hydrogen.

A complete list of commercially important aluminum compounds is given in "Aluminum Compounds and Uses."

## Production and Use

Bauxite is the starting material for the commercial production of refined aluminum oxide, known commonly as alumina, and aluminum metal. Most of the bauxite processed in the United States is imported, chiefly from Jamaica and Surinam. Virtually all domestic bauxite is mined in Arkansas. Alumina is prepared by dissolving the bauxite in aqueous NaOH to form soluble sodium aluminate. After removing the insoluble impurities, the solution is cooled and aluminum hydrate is precipitated by seeding. The aluminum hydrate is collected and calcined at 1,200°C, yielding alumina. This is known as the Bayer process.

Metallic aluminum is produced commercially by the electrolytic reduction of pure aluminum oxide in a bath of molten cryolite ($3NaF \cdot AlF_3$). Synthetic cryolite is currently used, due to depletion of the natural supply. It takes 2.26 tons of dry bauxite to yield 1 ton of pure $Al_2O_3$, and 1.817 tons of pure $Al_2O_3$ is necessary for the production of 1 ton of the pure metal.

Aluminum is also recovered from old and new scrap aluminum, aluminum alloys, and aluminum chemicals for secondary production.

Aluminum sulfates and other chemicals are generally produced directly from bauxite or other aluminum minerals by conversion with acids. More highly purified chemicals can be produced from alumina. Aluminum chloride can be produced by mixing alumina and hyprochlorous acid, but the chief mode of production is by reacting molten aluminum metal with chlorine gas.

Alkyl aluminum compounds are prepared by direct synthesis using the appropriate alkyl compounds and aluminum hydride, $AlH_3$, prepared by reacting powdered aluminum metal with hydrogen. Due to the present availability of cheap olefins, this synthesis is economical on a large scale.

Figure 1 shows the production pathways for aluminum compounds. Available production and consumption data for aluminum compounds are given in Tables 1 and 2.

## Aluminum Compounds and Uses

**Bauxite:** Starting material for other aluminum compounds; can also be utilized without further chemical conversion in production of abrasive materials and refractory fire brick.

**Aluminum metal:** Structural material for diverse applications, food processing apparatus, reducing agent in thermite process to obtain other metals from their oxides.

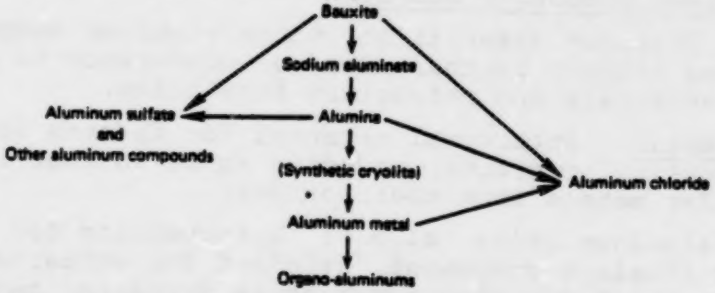


Figure 1. Production of Pathways of aluminum compounds. (Source: SRI, 1976)

Table 1. Bauxite Production and Consumption Statistics (millions of tons)

| Bauxite production | | | Bauxite consumption | | | |
|---|---|---|---|---|---|---|
| U.S. production | | Imports | For alumina | For chemicals directly from bauxite | Abrasives | Refractory |
| 1960 | 1.998 | 8.739 | 8.141 | 304 | 204 | 94 |
| 1961 | 1.228 | 9.206 | 8.034 | 234 | 188 | 112 |
| 1962 | 1.369 | 10.573 | 9.878 | 244 | 261 | 138 |
| 1963 | 1.525 | 9.212 | 10.596 | 249 | 230 | 179 |
| 1964 | 1.601 | 10.188 | 11.769 | 255 | 240 | 219 |
| 1965 | 1.654 | 11.199 | 12.622 | 261 | 266 | 298 |
| 1966 | 1.798 | 11.529 | 13.108 | 294 | 296 | 313 |
| 1967 | 1.654 | 11.594 | 12.578 | 305 | 246 | 315 |
| 1968 | 1.685 | 10.976 | 13.165 | 326 | 225 | 311 |
| 1969 | 1.843 | 12.163 | 14.574 | 318 | 234 | 366 |
| 1970 | 2.082 | 12.628 | 14.653 | 307 | 280 | 370 |
| 1971 | 1.988 | 12.326 | 14.632 | 319 | 307 | 380 |
| 1972 | 1.812 | 11.428 | 14.359 | 294 | 253 | 403 |
| 1973 | 1.879 | 12.778 | 15.505 | 313 | 259 | 496 |
| 1974 | 1.969 | 14.308 | 15.646 | 341 | 295 | 539 |

(Source: SRI, 1976)

Table 2. Production of Aluminum and Aluminum Chemicals (millions of tons)

| | Primary aluminum | Secondary aluminum | U.S. alumina | Alumina imports | Aluminum chloride | Aluminum sulfate |
|---|---|---|---|---|---|---|
| 1960 | 2,014 | 329 | 3,896 | -- | 31.2 | 533 |
| 1961 | 1,904 | 340 | 3,699 | -- | 28.8 | 541 |
| 1962 | 2,118 | 462 | 4,402 | -- | 31.7 | 563 |
| 1963 | 2,313 | 506 | 4,817 | -- | 32.6 | 576 |
| 1964 | 2,553 | 552 | 5,319 | -- | 38.0 | 610 |
| 1965 | 2,755 | 641 | 5,577 | 227 | 40.6 | 642 |
| 1966 | 2,986 | 693 | 5,884 | 488 | 42.9 | 679 |
| 1967 | 3,269 | 698 | 6,046 | 952 | 44.0 | 665 |
| 1968 | 3,255 | 817 | 5,859 | 1,316 | 42.4 | 716 |
| 1969 | 3,793 | 901 | 6,672 | 1,887 | 46.2 | 758 |
| 1970 | 3,976 | 781 | 6,563 | 2,555 | 37.8 | 723 |
| 1971 | 3,925 | 816 | 6,445 | 2,175 | 34.7 | 722 |
| 1972 | 4,122 | 946 | 6,204 | 2,850 | -- | 798 |
| 1973 | 4,529 | 1,038 | 6,785 | 3,375 | -- | 845 |

## Aluminum Compounds and Uses

Bauxite: Starting material for other aluminum compounds; can also be utilized without further chemical conversion in production of abrasive materials and refractory fire brick.

Aluminum metal: Structural material for diverse applications, food processing apparatus, reducing agent in thermite process to obtain other metals from their oxides.

Alumina (aluminum oxide, $Al_2O_3$): Intermediate for aluminum metal and other aluminum compounds, calcined for abrasive materials, refractory brick for high-temperature furnaces, ceramics, absorbent, drying agent, catalyst for organic chemistry, cosmetics, pigments, paper coatings, electronic equipment, filler in plastics and resins.

Aluminum sulfate: Antiperspirant, water purification, mordant in dyeing, lubricating compositions, tanning, deodorizer and decolorizer, ore flotation, cosmetics, pharmaceuticals, pigments, paper sizing.

Ammonium, potassium, and sodium alum: Baking powder, medicine, mordant in dyeing, dressing of hides, water purification, paper sizing.

Aluminum hydroxide: Absorbent, catalyst, ceramics, mordant in dyeing, paper sizing, water purification, waterproofing, cosmetics, medicinals.

Aluminum chloride: Catalyst for organic reactions, cosmetics, antiperspirant, antiseptic, wool carbonizing, photofixing baths, wood preservative.

Sodium aluminate: Paper sizing, water treatment, cleaning compositions, mordant in dyeing, sewage treatment, clarification of sugar, welding fluxes, delustering of rayon, enamel slips.

Aluminum phosphate: Organic catalyst, ceramics, glass manufacture, dental cements, high-temperature bonding agent for refractories.

Aluminum fluoride: Production of aluminum metal, ceramics, repressant of alcoholic side fermentations, organic catalyst.

Triethyl aluminum, triisobutyl aluminum, diisobutyl aluminum hydride: Polymerization cocatalysts for production of polyolefins, reducing agents, initiators for syntheses of linear alpha-olefins and linear primary alcohols.

Aluminum acetate solution: Astringent, antipruritic, antiseptic.

Aluminum bis(acetylsalicylate): Analgesic, antipyretic.

Aluminum borate: Polymerization catalyst, glass manufacture.

Aluminum borohydride: Reducing agent, preparation of other borohydrides, jet and rocket fuel additive.

Aluminum bromide: Acid catalyst in organic synthesis.

Aluminum calcium hydride: Reducing agent.

Aluminum carbide: Generating methane, reduction of metal oxides, manufacture of aluminum nitride.

Aluminum chlorate: Antiseptic, astringent.

Aluminum diacetate: Manufacture of color lakes, waterproofing and fireproofing fabrics, antiperspirant, disinfectant.

Aluminum ethoxide: Reducing agent, polymerization catalyst.

Aluminum hydride: Polymerization catalyst, reducing agent, preparation of other metal hydrides.

Aluminum hydroxychloride: Astringent, antiperspirant.

Aluminum isopropoxide: Organic syntheses, manufacture of aluminum soaps, paints, and textile waterproofing.

Aluminum lactate: Foam fire extinguishers, dental impression materials.

Aluminum lithium hydride: Reducing agent, preparation of other hydrides.

Aluminum nitrate: Leather tanning, antiperspirant, corrosion inhibitor, uranium extraction, nitrating agent.

Aluminum oleate: Lacquer for metals, sizing agent, waterproofing, high-temperature grease.

Aluminum palmitate: Thickening agent for lubricants, waterproofing, sizing and glazing paper and leather.

Aluminum silicate: Dental cements, glass manufacture, manufacture of semiprecious stones, enamels, and ceramics.

## Health Aspects

Aluminum is present in plant and animal matter and is used in food processing apparatus and containers; as a result amounts of up to 200 mg are estimated to be ingested daily by humans (Campbell et al., 1957). Aluminum is not readily absorbed through the intestine, and only trace amounts appear in tissues (Campbell et al., 1957). Ondreicka and his associates (1966) found that rats fed a diet containing 2,835 ppm aluminum retained 20 times as much aluminum as those fed a normal diet. Accumulation was highest in the skeleton, liver, adrenals, and testes. Chronic dosing of rats and mice at 350 ppm in diet caused growth stunting in the second and third generations. Additional effects of chronic and acute aluminum poisoning were interference with intestinal phosphate absorption and inhibition of phosphorylation mechanisms for incorporation of phosphorus into DNA, RNA, ATP, and phospholipids (Ondreicka et al., 1966). High levels of dietary aluminum may also cause rickets due to the movement of bone phosphorus to the serum to counteract the decreased availability of ingested phosphorus (Underwood, 1973). High doses of aluminum hydroxide, as used for an antacid or in therapy for renal caliculi, produce no symptoms other than mild gastrointestinal irritation (Campbell et al., 1957). The disruption of phosphate metabolism is a potential cause for alarm, and extensive removal of phosphate from bones could seriously weaken susceptible individuals, but no symptoms of toxicity are produced from normal dietary intake of aluminum.

Aluminum salts have long been the substances of choice in antiperspirant solutions. Solutions of 5% $AlCl_3$ (Landsdown, 1974) and 10% $Al_2(NO_3)_3$ (Landsdown, 1973) applied to the skin of mice, rabbits, and pigs caused dermal irritation due to the affinity of the $Al^{+3}$ ion for skin keratin in acid solutions. Compounds showing no irritancy, except to highly sensitive skin, include 25% solutions of aluminum chlorhydrate (the most extensively used antiperspirant) and 10% solutions of aluminum hydroxide, acetate, and sulfate (Landsdown, 1973). The mechanism of the antiperspirant activity is not understood.

The effects of inhalation of aluminum dusts and powders are not completely understood. Goralewski (1947) reported acute pulmonary degeneration in workers in an aluminum powder stamping mill, with extensive pulmonary fibrosis in several cases. The powders were coated with mineral oils to prevent aggregation. Pulmonary fibrosis has also been reported in England in workers exposed to stearin-coated powders (McLaughlin et al., 1962; Mitchell et al., 1961). Fibrosis has been reported in rats injected intratracheally with fine aluminum dusts, both coated and uncoated, but not with granular dusts (Corrin, 1963). These observations are countered by studies by Crombie and associates (1944), who found that workers in an aluminum stamping mill in Pittsburgh had as good health as any others in the plant. Crombie et al. also experimented with aluminum powder as treatment for silicosis. Of 34 men receiving 200-300 treatments with the powder, 19 showed clinical improvement in breathing capacity, while the condition of the other 15 stabilized. Fine metallic aluminum powders inhaled by hamsters, rats, and guinea pigs caused no fibrosis, but reversible alveolar proteinosis was present in all species. Intratracheal injection did produce focal pulmonary fibrosis, an effect which was probably due to physical irritation from this mechanism of exposure (Gross et al., 1973). Some of the discrepancies in the reported effects could be due to the different types of powders and different coatings that have been investigated, but harmful effects seem obvious, even if only mechanical. Other lung afflictions have been reported from exposure to various dusts in the aluminum industry, but since most aluminum minerals contain silicates as well as alumina, the causative mechanisms are unclear.

The American Conference of Governmental Industrial Hygienists (1974) rates $Al_2O_3$ an inert particulate, with a TLV of 3 million particles per cubic foot. No exposure limit for airborne aluminum metal has been established. In view of the conflicting evidence and the many unquestionable dangerous effects reported, it cannot be denied that inhaled aluminum powders are potentially debilitating and conditions producing them should be strictly monitored.

Metallic aluminum has been tested for carcinogenic activity, with no tumors resulting (Furst, 1971).

Alkyl aluminum compounds are extremely dangerous. Contact with skin produces immediate deep painful burns. Inhalation of vapors is destructive to lung tissue, and the fumes of the combustion products are also toxic. All these materials present a serious hazard to human health.

Aluminum in water at concentrations of over 1.5 ppm causes physiological and behavioral aberrations and acute mortality in rainbow trout (Freeman and Everhart, 1971). $AlCl_3$ at 44 ppm in seawater is harmless to marine organisms, 88 ppm is fatal to most fish, and 132 ppm is universally lethal to all organisms except sporulative bacteria (Pulley, 1950).

Aluminum chloride hexahydrate has been evaluated for toxicity to goldfish and the narrowmouth toad. One ppm (expressed as aluminum, in water pH 7-8) was the $LC_{50}$ concentration for newly hatched goldfish, while 75 ppm was lethal to all individuals. Four days after hatching, the $LC_{50}$ for goldfish was 0.5 ppm and the $LC_{100}$ was 5 ppm, with some anomalous effects appearing in the 0.001- to 0.01-ppm range. Tests on newly hatched toads gave an $LC_{50}$ value of 0.1 ppm and an $LC_{100}$ value of 10 ppm. Four days after birth, the $LC_{50}$ was between 0.05 and 0.1 ppm and the $LC_{100}$ about 0.5 ppm, with anomalous effects occurring at concentrations between 0.01 and 0.05 ppm. Most of these values are within the natural range for dissolved aluminum and place the toxicity of aluminum about equivalent to that of zinc; that is, less toxic than cadmium or mercury, but more toxic than selenium or arsenic (Black, 1976).

Aluminum is present in all soils from the decomposition of clays and other aluminum-containing minerals. At low pH it is present as the free trivalent ion. As the pH rises past 4, it begins to precipitate out as hydroxide. In the presence of phosphate, solubility is further decreased, with virtually complete precipitation by pH 4.4. In alkaline conditions (pH > 8), aluminum reappears in solution, but this does not represent any actual environmental conditions.

Many studies have demonstrated the toxic effect of aluminum on plants at soil pH values below 5. Potatoes grown in medium with aluminum concentrations above 5 ppm showed reduced vegetative growth and lower total tuber production by weight (Lee, 1971). Dry plant matter production from several grasses grown at soil concentrations of aluminum higher than 100 kg/hectare decreased significantly in similar studies using soils of varying acidity (Hutchinson and Hunter, 1970). The toxic effects are exhibited most markedly in roots as elongation is sharply curtailed (Rorison, 1958; Clarkson, 1966). Possible mechanisms for this effect include phosphate starvation due to precipitation of aluminum phosphates in the soil or in cell-free spaces in the roots (Rorison, 1958), direct inhibition of mitotic division in the root tip (Clarkson, 1966), or the loss of elasticity in the cell walls due to the aluminum-induced precipitation of pectins (Rorison, 1958). Liming of soil to pH 6 reduces the aluminum solubility to a point where it no longer affects plant growth (Hutchinson and Hunter, 1970).

## Environmental Aspects

In the Bayer process of purifying alumina, large amounts of $Al_2O_3$ dust are released. Because of the economic value of these particulates, efficient control procedures including multiple cyclones, electrostatic precipitators, and wet scrubbers are used. In the electrolytic reduction of alumina to aluminum, various gaseous and solid fluorides as well as other particulates, depending on the type of cell used, are produced. The gaseous effluents are fairly efficiently controlled by such techniques as spray towers and floating bed scrubbers, as well as a pathway in which the alumina feed adsorbs the fluorides, which then reenter the reduction bath. These techniques, plus cyclones, also remove most of the particulates. The degree of efficiency of these systems is largely determined by how well the effluent gases from the cell can be contained, and cell types best adapting themselves to these controls are being favored. Most of the emissions are returned to the production process, although some, especially fluorides, may appear in wastewater.

Alum and aluminum sulfate have been used as coagulants and clarifying agents in water treatment facilities, resulting in precipitation of 80% of the bacteria in organic matter. Dissolved aluminum concentrations are usually lowered in waters treated by these methods (Campbell et al., 1957). Other sources of aluminum in wastewater include mining operations, the chemical industries, the dye and pigment industries, paper mills, textile plants, and dyeing and tanning factories. Because of the very low solubility of aluminum hydroxide at normal pH levels, almost all aluminum ions entering the water systems will promptly precipitate out as the hydroxide. This situation may lead to increased localized deposits of aluminum hydroxide, but there are no data which show that this occurs. Monitoring of various water systems has shown that the aluminum content of drinking water rarely exceeds 1 ppm and is more likely to be below 0.5 ppm. Waters from mine drainage contain no higher levels, but weathering of rocks with acid waters can give levels of 10-20 ppm. Acid mineral springs may contain several hundred ppm. These levels would apparently present potential dangers to sensitive fish such as rainbow trout, but no incidents of fish kills due to aluminum have been reported.

Use of recyclable aluminum beverage cans is a viable alternative to the use of reusable bottles for prevention of solid waste problems. In 1974, 2.3 billion cans worth about $13 million were returned for reprocessing. This was estimated at about 35% of the aluminum cans produced. To be competitive with reusable bottles, a recycling program would need to return about 90% of the cans, indicating that more public cooperation in this area will be necessary since without effective recycling programs, aluminum cans are a solid waste problem themselves.

Organoaluminum compounds cannot exist in the environment since their extreme reactivity would result in immediate destruction upon contact with air or water. The stringent care necessary for safe handling of these materials in industrial use also serves to prevent their release.

## REFERENCES

American Conference of Governmental Industrial Hygienists. Documentation of the Threshold Limit Values. 1974.

Black, Jeffery. University of Kentucky, personal communication. 1976.

Campbell, I. R., J. S. Cass, J. Cholak, and R. A. Kehoe. Aluminum in the environment of man. AMA Arch. Ind. Health 15:359-448, 1957.

Clarkson, D. T. Aluminum tolerance within the species Agrostis. J. Ecol. 54:167-178, 1966.

Corrin, B. Aluminum pneumoconiosis. II. Effect on the rat lung of intratrachear injection of stamped alumina powders containing different lubricating agents and a granular aluminum powder. Br. J. Ind. Med., vol. 20, 1973. (As cited by Gross et al., 1973)

Crombie, D. W., J. L. Blaisdell, and G. MacPherson. The treatment of silicosis by aluminum powder. Can. Med. Assoc. J. 50: 318-328, 1944.

Freeman, R. A., and W. H. Everhart. Toxicity of aluminum hydroxide complexes in neutral and basic media to rainbow trout. Trans. Am. Fish Soc. 100(4):644-658, 1971.

Furst, A. Trace elements related to specific chronic diseases: Cancer. Geol. Soc. Am. Memoir 123:109-130, 1971.

Goralewski, G. Arch. Gewerbepathol. Gewerbe Hyg., vol. 9-11, 17, 1939-41, 1943.

Gross, P., R. Harley, and R. A. deTreville. Pulmonary reaction to metallic aluminum powders. Arch. Environ. Health 26(5):227-236, 1973.

Hutchinson, F. E., and A. S. Hunter. Exchangeable aluminum levels in two soils as related to lime treatment and growth of six crops species. Agron. J. 62(6):702-704, 1970.

Industrial Hygiene and Toxicology. New York, Interscience Publishers. 1963.

Jones, H. R. Pollution Control in the Nonferrous Metals Industry. Park Ridge, N.J., Noyes Data Corp. 1972.

Kirk-Othmer Encyclopedia of Chemical Technology. New York, Interscience Publishers. 1974.

Landsdown, A. B. G. Aluminum compounds in the cosmetics industry. Their action as antiperspirants and safety in use. Soap Perfume Cosmet. 47(5):209-212, 1974.

Lee, C. R. Influence of aluminum on plant growth and tuber yield of potatoes. Agron. J. 63(3):363-364, 1971.

McLaughlin, A. L. G. et al. Pulmonary fibrosis and encephalopathy associated with the inhalation of aluminum dust. Br. J. Ind. Med., vol. 19, 1962. (As cited by Gross et al., 1973).

Mitchell, J. Pulmonary fibrosis in workers exposed to finely powdered aluminum. Br. J. Ind. Med., vol. 18, 1961. (As cited by Gross et al., 1963).

Ondreicka, R., E. Ginter, and J. Kortus. Chronic toxicity of aluminum in rats and mice and its effects on phosphorus metabolism. Br. J. Ind. Med. 23:305-312, 1966.

Perry, K.M.A. Diseases of the lung resulting from occupational dusts other than silica. Thorax 2:91-120, 1947.

Pulley, T. E. The effect of aluminum chloride in small concentrations on various marine organisms. Tex. J. Sci. 2(3): 405-411, 1950.

Rorison, I. H. The effect of aluminum on legume nutrition. Proc. Univ. of Nottingham Easter School of Agr. Sci. 5:43-61, 1958.

Stanford Research Institute. 1976. Chemical Economics Handbook. Menlo Park, Calif.

Underwood, E. J. Trace elements. Toxicants Occurring Naturally in Food 2:43-87, 1973.

Water Quality Criteria Data Book, Vol. 2. Inorganic Chemical Pollution of Freshwater. Cambridge, Mass., Arthur D. Little, Inc. 1971.

# CHEMICAL HAZARD INFORMATION PROFILE

## Aniline

Date of report: January 20, 1978

This chemical was chosen for study because of its high production volume.

It is recommended that OTS wait for completion of the scheduled NIOSH Criteria Document and the NCI carcinogenicity study before initiating any further evaluation of aniline. This CHIP should be updated based on the additional information.*

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

### Chemical Identity

Aniline (phenylamine, aminobenzene) is a colorless, oily liquid having a boiling point of 184°C. Aniline is miscible with alcohol, benzene and chloroform; it is soluble in water (Stecher, 1969; Weast, 1971).

### Production and Use

Aniline is produced commercially by the reduction of nitrobenzene or the ammonolysis of chlorobenzene (Lowenheim and Moran, 1975). Annual domestic production of aniline is currently around 500 million lb. The major producers of aniline are American Cyanamide Co. (two plants; West Virginia and New Jersey), E. I. du Pont de Nemours (two plants; Texas and New Jersey), First Mississippi Corp. (one plant; Mississippi) and Rubicon Chemicals, Inc. (one plant; Louisiana) (SRI, 1977).

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*Subsequent to the review of this CHIP document and the selection of the tentative dispositions given above, the TSCA Interagency Testing Committee recommended aniline for primary consideration for possible testing under section 4(a) of TSCA (44 FR 31866, June 1, 1979).

Table 1. Aniline Consumption Pattern (%)

| | % |
|---|---|
| Isocyanates | 40 |
| Rubber chemicals | 35 |
| Dyes and intermediates | 6 |
| Hydroquinone | 4 |
| Drugs | 4 |
| Miscellaneous | 9 |

Source: SRI, 1977.

As can be seen from Table 1, aniline is most commonly used as a chemical intermediate for the production of other products. Miscellaneous uses of aniline include: production of resins (formaldehyde, furfural, epoxy, and others); corrosion inhibitor to protect some metals from attack by wet carbon tetrachloride; manufacture of explosives, phenolics, surfactants, herbicides, fungicides, diphenylamine, varnishes, and perfumes; in textile, paper, metallurgical, and petroleum refining industries; catalyst; stabilizer (especially as polymerization inhibitor); intermediate in dye industry (Stecher, 1969; CCD, 1977; Kouris and Northcott, 1967).

## Health Aspects

Methemoglobinemia is the most prominent symptom of aniline poisoning in man (Hamblin, 1963). The symptoms of the toxic methemoglobinemia are those of oxygen lack proportional to the percentage of hemoglobin that is tied up. Levels of methemoglobin below 20% generally cause no symptoms; 20-50% methemoglobin can result in dyspnea, tachycardia, headache, and dizziness; concentrations above 60-70% may produce coma and death (Harrison, 1977).

Inhalation of 7-53 ppm of aniline vapor causes only slight symptoms of methemoglobinemia, while exposure to concentrations in excess of 100-160 ppm for over 1 hr can cause serious difficulty (Henderson and Haggard, 1943).

IARC (1973) reviewed the carcinogenicity data on aniline and concluded that the presently available information appears to indicate that aniline is not a human or animal carcinogen. McCann et al. (1975) reported that aniline was negative in the Ames test for mutagenicity.

## Environmental Aspects

MITRE Corp. (1976), in an EPA-sponsored report, estimates that 6.15 million lb of aniline was released to the environment in 1974. The U.S. production of aniline for that year totaled 551 million lb.

Aniline in the atmosphere reacts photochemically to form N-methylaniline, N,N-dimethylaniline, acetanilide, isomeric hydroxyanilines, and phenols (MITRE Corp., 1976). (The first four compounds can cause methemoglobinemia in similar fashion to that seen with aniline °Sax, 19751.)

In a model ecosystem, aniline (0.01-0.1 ppm) was rapidly and completely detoxified to polar metabolites by Daphnia and freshwater snails. Algae and mosquito larvae, however, were found to retain N-methyl- and N,N-dimethylaniline, respectively. Mosquito fish retained small amounts of unchanged aniline (with ecological magnification) and other metabolities (Lu and Metcalf, 1975).

Aniline is fairly toxic to nitrifying bacteria such as *Nitrosomas* sp. and *Nitrobacter* sp. A concentration of 7.7 mg/l of aniline inhibits nitrification in activated sludge by approximately 75% (Tomlinson et al., 1966).

Aniline degrades readily in soil, as it has a half-life of less than 1 week (Thompson, 1969).

### REFERENCES

CCD (Condensed Chemical Dictionary), 9th ed. New York, Van Nostrand Reinhold Co. 1977.

Hamblin, D. O. Aromatic nitro and amino compounds. *In* F. A. Patty (ed.). Industrial Hygiene and Toxicology. 2nd ed. New York. Interscience Publishers. 1963. p. 2105.

Harrison, M. R. Toxic methemoglobinemia. Anaesthesia 22:270, 1977.

Henderson, Y., and H. W. Haggard. Noxious Gases, 2nd ed. New York, Reinhold Publishing Co. 1943. As cited in Documentation of the TLV, ACGIH, 1971.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of the Carcinogenic Risks of Chemicals to Man, vol. 4. 1973. p. 27.

Kouris, C. S., and J. Northcott. Aniline and its derivatives. *In* Kirk-Othmer Encyclopedia of Chemical Technology, vol 2. 1967. p. 411.

Lowenheim, Frederick A., and Marguerite K. Moran. Faith, Keyes, and Clark's Industrial Chemicals. New York, John Wiley and Sons. 1975.

Lu, P. Y., and R. L. Metcalf. Environmental fate and biodegradability of benzene derivatives as studied in a model ecosystem. Environ. Health Perspect. 10:269, 1975.

McCann, Joyce et al. Detection of carcinogens as mutagens in the Salmonella/microsome test: Assay of 300 chemicals. Proc. Natl. Acad. Sci. U.S.A. 72(12):5135, 1975.

MITRE Corp. Scoring of Organic Air Pollutants. Chemistry, Production, and Toxicity of Selected Synthetic Organic Chemicals. 1976. *

Sax, N. Irving. Dangerous Properties of Industrial Materials, 4th ed. New York, Van Nostrand Reinhold Co. 1975.

SRI (Stanford Research Institute). Chemical Economics Handbook. Menlo Park, Calif. 1977.

Stecher, P. G. (ed.). The Merck Index, 8th ed. Rahway, N.J., Merck and Co. 1969.

Thompson, F. R. Persistence and effects of some chlorinated anilines on nitrification in soil. Can. J. Microbiol. 15(7):791, 1969.

Tomlinson, T. G. et al. Inhibition of nitrification in the activated sludge process of sewage disposal. J. Appl. Bacteriol. 29(2):266, 1966.

Weast, Robert C. (ed.). CRC Handbook of Chemistry and Physics, 52nd ed. Cleveland, Chemical Rubber Co. 1971.

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*This document was prepared for the U.S. Environmental Protection Agency by the MITRE Corp. It is a secondary source and does not cite its primary references. Thus, verification of some information is not possible. The environmental release data were taken from the NSF/Rann Research Program on Hazard Priority Ranking of Manufactured Chemicals.

# CHEMICAL HAZARD INFORMATION PROFILE

## Benzyl Chloride

Date of report: December 9, 1977

This chemical was chosen for study because of its relatively high production volume.

It is recommended that TSCA Section 8(a) and 8(d) submissions be required for benzyl chloride. More definitive information on exposure potential is needed as well as additional information to supplement the relatively scanty data on health effects. A contractor literature search on environmental aspects is recommended because very little information was found in the preparation of this report. This Chemical Hazard Information Profile should be updated based on the additional data obtained.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

## Chemical Identity

Benzyl chloride ($C_6H_5CH_2Cl$) is a colorless, highly refractive liquid with a pungent aromatic odor. It freezes at -39°C and boils at 179.4°C. The density of benzyl chloride is 1.1002 at 20°C. The vapor pressure of benzyl chloride is 1.4 mm at 25°C. It is immiscible in water, but decomposes in hot water to give benzyl alcohol. At room temperature it is miscible with ethanol, ether, and chloroform. Its explosive limit in air is lower than 1.1% by volume. It is considered a moderate fire hazard and a moderate explosion hazard (violent with metals) (Lowenheim and Moran, 1975, and other sources). Benzyl chloride is a dangerous disaster hazard since it will react with water or steam to produce toxic and corrosive fumes; it can react vigorously with oxidizing materials (Sax, 1968). Synonyms for benzyl chloride include alpha-chlorotoluene and alpha-tolyl chloride.

## Production and Use

The only processes in commercial use in the United States for the manufacture of benzyl chloride are the direct chlorination of boiling toluene in the dark and the photochlorination of toluene. Boiling toluene is chlorinated in the dark until there is a 37.5% increase in weight. The reaction mixture is then agitated with mild alkali and distilled. Benzal chloride and benzotrichloride are formed as by-products of benzyl chloride in a ratio of 1:0.1:10. In the photochlorination process, chlorination is continued until a 20 to 25% weight increase in the reaction mixture is achieved. Using this procedure, it is possible to avoid the formation of benzotrichloride. In this case the ratio of benzyl chloride to benzal chloride is 10:1 (Lowenheim and Moran, 1975).

The still bottoms of benzyl chloride production are a hazardous waste discharge to land disposal and contain 0.001 kg of highly dangerous components (benzyl chloride and benzotrichloride) per kg of benzyl chloride produced (Gruber, 1976).

The major commercial producers of benzyl chloride and their capacities (as of December 1975) are:

| Producers | Capacity (millions of lb/yr) |
|---|---|
| Monsanto, Bridgeport, N.J. | 75 |
| Stauffer, Edison, N.J. | 11 |
| Tenneco, Fords, N.J. | 9 |
| Total | 95 |

Monsanto had plans to bring another benzyl chloride plant on stream at East St. Louis, Mo. (Sauget, Ill., according to CEH, November 1976) in 1977 to feed a new benzyl butyl phthalate plant. The plant capacity was expected to be at least 75 million lb per year. The annual demand for benzyl chloride was 90 million lb in 1975 (Chemical Marketing Reporter, December 12, 1975). Benzyl chloride is available commercially in an anhydrous form or stabilized with aqueous sodium carbonate solution (Hawley, 1977).

Major uses of benzyl chloride are benzyl butyl phthalate, 67%; benzyl alcohol, 13%; quarternary amines, 12%; and other uses, 8% (Chemical Marketing Reporter, December 12, 1975).

Benzyl butyl phthalate is used as a plasticizer in the manufacture of flexible vinyl, especially floor coverings. Growth in demand for flexible vinyl, and hence for benzyl butyl phthalate, is expected to continue. Benzyl alcohol is used as a dye assist, as a photographic developer, and in making pharmaceuticals and perfumes. Benzyl chloride serves as a raw material for disinfectants, bactericides, perfumes, and pharmaceuticals. Benzyl chloride may be used in synthetic tannins and synthetic penicillin, as a gasoline gum inhibitor, and as an intermediate in other processes. Benzyl chloride is also used as an intermediate in the production of benzyl acetate, benzyl cyanide, benzyl salicylate, and benzyl cinnamate. Use of benzyl chloride as an irritant gas has been reported (IARC, 1976).

## Health Aspects

The TWA established by OSHA for benzyl chloride in air is 1 ppm. (Soviet standard for benzyl chloride in the work place is 0.1 ppm [Hoecker et al., 1977].) The 96-hr aquatic toxicity rating is 10 to 1 ppm. The $LD_{50}$ for oral administration of benzyl chloride is 1,231 mg/kg for rats and 1,624 mg/kg for mice. Inhalation of benzyl chloride vapors by mice and rats gives $LC_{50}$ values of 80 and 150 ppm, respectively, for 2 hr of exposure (NIOSH, 1976). Reaction of guinea pigs to dermal application of benzyl chloride indicates that it is a strong sensitizing agent (Hoecker et al., 1977). Benzyl chloride has been found to be weakly mutagenic in *Salmonella typhimurium* (TA100) after treatment with 2 mg benzyl chloride per plate in the Salmonella/microsome test (McCann et al., 1975).

Benzyl chloride is absorbed by the lungs and the digestive tract. It appears to be metabolized to benzyl mercapturic acid following injection in rats and rabbits and oral administration in dogs. Following oral administration in rabbits, it is excreted in the urine as mercapturic acid and benzoic acid (IARC, 1976).

Fourteen week-old rats were given subcutaneous injections of 40 mg/kg benzyl chloride in arachis oil for 51 weeks. Three animals developed local sarcomas within 50 days. Of eight rats given 80 mg/kg benzyl chloride for 51 weeks, six developed local sarcomas in 500 days.

Most animals also developed lung metastases. Injection of arachis oil did not produce local tumors in control rats. Based on this information, the IARC considers benzyl chloride to be a carcinogen in rats.

Mice given intraperitoneal injections of benzyl chloride three times a week for 2 to 4 weeks (total dose of 600, 1,500, or 2,000 mg/kg) did not show significant changes in tumor incidence (Hoecker et al., 1977).

The human TCLo for inhalation of benzyl chloride has been found to be 16 ppm. This level of exposure was found to be intolerable within 1 min (ACGIH, 1971). Benzyl chloride is highly irritating to eyes, ears, nose, and throat and can cause lung edema. It may depress the central nervous system (ITII, 1976).

## Environmental Aspects

Benzyl chloride contamination of aquatic environments seems unlikely since it is reactive in water. Benzyl chloride reacts with oxidizing agents (Dorigan et al., 1976). Benzyl halides are considered very reactive, having a half-life (hydrolysis) of only a few minutes. Benzyl chloride is lipophilic as indicated by its log P value of 2.30 (Radding et al., 1977).

## REFERENCES

American Conference of Governmental Industrial Hygienists (ACGIH). Documentation of the Threshold Limit Values. 1971.

Chemical Marketing Reporter, December 12, 1975.

Dorigan, J. et al. Scoring of Organic Air Pollutants: Chemistry, Production and Toxicity of Selected Organic Chemicals. MITRE Corp. (for EPA). 1976.

Gruber, E. I. (Project Manager). Assessment of Industrial Hazardous Waste Practices, Organic Chemicals, Pesticides, and Explosives Industries. U.S. Environmental Protection Agency. 1976.

Hawley, Gessner G. Condensed Chemical Dictionary, 9th ed. New York, Van Nostrand Reinhold Co. 1977.

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*This document was prepared for the U.S. Environmental Protection Agency by the MITRE Corp. It is a secondary source and does not cite its primary references. Thus, verification of some information is not possible. The environmental release data were taken from the NSF/Rann Research Program on Hazard Priority Ranking of Manufactured Chemicals.

Hoecker, Jane E. et al. Information Profiles on Potential Occupational Hazards. Center for Chemical Hazard Assessment (for NIOSH). 1977.

IARC (International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, vol. II. Lyon, France. 1976. p. 217-221.

International Technical Information Institute (ITII). Toxic and Hazardous Industrial Chemicals Safety Manual. Tokyo. 1976.

Lowenheim, Frederick, and Marguerite Moran. Faith, Keyes and Clark's Industrial Chemicals, 4th ed. New York, John Wiley & Sons, Inc. 1975.

McCann, Joyce et al. Detection of carcinogens as mutagens in the Salmonella/microsome test: Assay of 300 chemicals. Proc. Natl. Acad. Sci. U.S.A. 72(12):5135-5139, 1975.

NIOSH. Registry of Toxic Effects of Chemical Substances, 1976 ed.

Radding, Shirley B. et al. Review of the Environmental Fate of Selected Chemicals. Stanford Research Institute (for EPA). May 1977.

Sax, N. Irving. Dangerous Properties of Industrial Materials, 3rd ed. New York, Van Nostrand Reinhold Co. 1968.

Stanford Research Institute (SRI). Chemical Economics Handbook. Menlo Park, Calif. 1976.

Stanford Research Institute. Directory of Chemical Producers. Menlo Park, Calif. 1975.

# CHEMICAL HAZARD INFORMATION PROFILE

## Bromine and Bromine Compounds

Date of report: November 1, 1976

This group of chemicals was chosen for study because of a report describing damage to vegetation near bromine production facilities.

It is recommended that this group of chemicals be considered for further testing needs. The high potential for the development of new bromine compounds and new uses for old compounds is the impetus for testing consideration.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

## General Information, Production, and Consumption

Bromine belongs to the group of nonmetallic elements known as the halogens, which includes fluorine, chlorine, iodine, and the extremely rare element astatine. Elemental bromine exists in the diatomic form, $Br_2$, and it is a volatile liquid at ordinary room temperature (boiling point 58.8°C at atmospheric pressure). Bromine is a strong oxidizing agent similar to but weaker than chlorine. The most stable valence states of bromine are -1 and +5, although valence states of +1 and +3 are also known.

Bromine is widely distributed in nature in both the solid portion of the earth's crust (1.6 ppm) and in ocean water (65 ppm by weight). Bromine is also abundant in the waters of salt lakes found in closed basins and in the brines or saline deposits left by the evaporation of such salt lakes during earlier geologic periods. Brines serve as the primary source of bromine in the United States; seawater is used as a bromine source in other parts of the world but not, at this time, in the United States.

Eighty percent of the bromine produced in the United States is extracted from natural brines in the El Dorado-Magnolia area of southern Arkansas; most of the remainder is produced in Michigan (see Table 1).

Table 1. Domestic Bromine Producers, Plant Locations, and Capacities (1976)

| Company | Locations | Capacity ($10^6$ lb) |
|---|---|---|
| Arkansas Chemical Inc. | El Dorado, Ark. | 60 |
| Dow Chemical USA | Luddington, Mich. | 15 |
| | Magnolia, Ark. | 85 |
| | Midland, Mich. | 105 |
| Ethyl Corp. | Magnolia, Ark. | 160 |
| Great Lakes Chemical Corp. | El Dorado, Ark. | 95 |
| | Marysville, Ark. | 45 |
| Kerr-McGee Corp. | Trona, Calif. | 2 |
| Morton-Norwich Products, Inc. | Manistee, Mich. | Unknown |
| Northwest Industries, Inc. | El Dorado, Ark. | 25 |
| | St. Louis, Mich. | 5 |
| Total | | 597 |

Source: CEH, 1976.

Bromine exists as the bromide ion in these brines, and obtaining elemental bromine from them entails four essential steps: oxidation of the bromide in the brine to bromine, removal of bromine vapor from solution, condensation of the vapor, and, finally, purification of the product. Initially the brines are heated from the ground recovery temperature of 90°C to just below the boiling point of 107°C. Chlorine is added to oxidize the bromide ions and replace them in the brine. The released bromine is separated from the brine by "blowing out" with steam and is then purified by distillation and dried with sulfuric acid. The chlorine is recycled, and bromine recovery is generally in excess of 95% (Stenger, 1964; CEH, 1976).

Table 2 shows the annual production and consumption of bromine for recent years. As can be seen from these data, most of the elemental bromine is used to manufacture bromine-containing compounds. The largest end use of bromine, currently accounting for about 50-60% of bromine consumption, is for the production of ethylene dibromide (EDB), which is used primarily as a lead scavenger in gasoline. In past years, EDB has accounted for well over 90% of bromine consumption. The decline in EDB use in recent years has been due largely to the lowering of the lead content of gasoline and the conversion to nonleaded gasoline for newer model cars. The second largest end use of bromine is for the production of methyl bromide, which is used as a pesticide, soil and grain fumigant, and fire-extinguishing fluid.

The elemental bromine consumption data shown in Table 2 refer to that which is sold by primary producers. Some of this is used directly for such applications as a bleaching and disinfecting agent, swimming pool sanitation, and water purification; some is sold to other companies to be used in the production of bromine compounds.

The "Other" category in Table 2 includes the numerous organic and inorganic bromine compounds that are produced by too few companies for production data to be available from the International Trade Commission. In addition to elemental bromine itself, the major inorganic bromine compounds are hydrobromic acid and the bromide salts (potassium, sodium, and ammonium). Hydrobromic acid is used as an industrial chemical for the production of other bromine compounds; the alkalai bromides are used in the preparation of sedatives, medicines, and photographic emulsions. The end use of inorganic bromine compounds noted as having future growth potential is that of water and waste treatment. Elemental bromine, as noted above, and bromine chloride (BrCl) are the bromine compounds likely to be important in such applications.

There are many organic bromine compounds, both aliphatic and aromatic, which are available commercially for a variety of applications, including uses as intermediates, agricultural chemicals, photographic chemicals, dyes, inks, medicinals, hydraulic fluids, coolants, cosmetics, and reagents. The fastest growing end use for organic bromine compounds, however, is in the area of fire- and flame-retardant chemicals. Consumption of bromine for this end use has grown from 10 million lb in 1964 to 56 million lb in 1974, with the largest growth in the most recent years. Some of these compounds are used as fire-extinguishing agents (bromotrifluoromethane and bromochlorodifluoromethane), some are used as monomers for fibers, plastics, and foams (for example, tetrabromobisphenol A and tetrabromophthalic anhydride), and some are simple additives to synthetic resins (for example, tris[2,3-dibromopropyl] phosphate, though this compound is now being phased out).

Table 2. U.S. Reported Production, Imports, Exports, and Consumption of Bromine and Bromine Compounds[a] (millions of lb)

| | | | | % (bromine content) | | | |
|---|---|---|---|---|---|---|---|
| Year | $Br_2$ production | Imports | Exports | $Br_2$ | Ethylene dibromide | Methyl bromide | Other |
| 1970 | 350 | 0.14 | 8 | 7 | 73 | --[b] | 20 |
| 1971 | 356 | 0.01 | 20 | 9.5 | 68.5 | --[b] | 22 |
| 1972 | 387 | 0.05 | 30 | 9.5 | 70 | 5.5 | 15 |
| 1973 | 418 | 0.06 | 55 | 9.5 | 69.5 | 4.5 | 16.5 |
| 1974 | 432 | 0.02 | 69 | 11 | 59 | 4 | 26 |
| 1975 | 417 | 0.03 | 70 | -- | 92 | 8 | -- |

Source: CEH, 1976.

[a] Consumption as compounds sold by primary producers of bromine; $Br_2$ consumption for direct use and intermediate use by secondary users.

[b] Included in "Other" for 1970-71.

The most notable feature of the bromine industry at this time is its changing character with respect to outlets. The lack of market diversification in the past, when almost all of the bromine produced was converted to EDB, is now being overcome as the number of bromine compounds available and the specific applications of these are on the increase. The general trend appears to be toward continued, vigorous growth, particularly in the flame retardants market, and possibly significant growth in the area of water and waste treatment.

## Health and Environmental Problems

The following are brief discussions of the health and environmental problems relating to bromine that appear, from this preliminary investigation, to be of particular importance.

### Bromism

"Bromism" is the clinical term for the condition associated with excessive tissue levels of bromide ions. The symptoms of bromism are subtle, though well established: slowing of cerebration, impaired memory, anorexia, skin rash, headache, slurring of speech, confusion (Campbell, 1949), weakness, disturbed reflexes (Neiswander, 1958), drowsiness, and mild conjunctivitis (Woodbury, 1972). The blood bromide concentration needed to evoke the symptoms of bromism is dependent upon the individual; severe reactions are known to occur with bromide levels as low as 0.5 mg/ml of blood. Generally, however, intoxications of 0.5-1.5 mg/ml of blood are deemed moderate, while levels above 1.5 mg/ml are severe (Campbell, 1949).

The most common cause of bromism is the abuse of bromide-containing patent medicines, although occupational exposure (Shapovalov et al., 1974) and ingestion of well water with high bromide levels (Fried and Malek-Ahmadi, 1975) may also lead to the onset of the condition. Chronic exposure to a bromide source, even at low concentrations, may lead to bromism because of the long plasma half-life of the bromide ion. Woodbury (1972) estimates that the half-life of the ion in the human is at least 12 days. Ingested bromide ions are preferentially retained by the kidneys at the expense of chloride; thus chloride levels in the body are depressed in direct proportion to the bromide elevation. For instance, the CNS effects of bromism are traceable to bromide replacement of chloride ions in the brain. Bromism, however, does not result in permanent damage to the CNS or other body functions; with removal of the bromide source, recovery is generally rapid (Woodbury, 1972).

There is one instance reported in the literature of a possible teratogenic effect associated with bromism. Opitz et al. (1972) detail a woman who had two normal children prior to a 5-year bout with bromism. During the period of heaviest bromide intake, she had two boys who differed from the two siblings born previously. The two boys were short (second percentile for age) and had small heads (one was definitely microcephalic), and the microcephalic child had a congenital heart defect. Following this period, the woman was taken off bromides and gave birth to a normal boy.

The metabolism of bromides is closely related to the functioning of the thyroid gland in man. Bromide blocks the entry of iodide into the thyroid and, with chronic bromide administration, can lead to thyroid tissue hyperplasia, better known as goiter. Several of the effects of bromism are identical to those attributed to hypothyroidism.

### Toxicity of Organic Bromine Compounds

Organobromines tend to exhibit greater toxicity than inorganic bromine compounds. The effects associated with organobromine compounds include damage to the CNS, male reproductive system, kidneys, and liver. In addition, several organic bromide compounds have been implicated as mutagens and/or carcinogens.

A summary of the toxic effects of some common organic bromides follows:

(1) Methyl bromide--chronic exposure to low levels can be fatal due to CNS and kidney damage (Sax, 1968).

(2) Bromoform--has a narcotic effect similar to that of chloroform, but is more toxic to the liver (Sax, 1968).

(3) Ethyl bromide--less toxic than methyl bromide, but can damage the liver and kidneys (Sax, 1968).

(4) Ethylene dibromide (EDB)--affects the liver and kidneys (Sax, 1968); has been shown to damage the male reproductive system in bulls (Amir, 1973) and rats (Edwards et al., 1970).

(5) 1,2-Dibromo-3-chloropropane (Nemagon, DBCP)--chronic exposure leads to liver, kidney, and lung damage (Gleason et al., 1969); has been shown to affect the male reproductive system in rats (Gleason et al., 1969; Faidysh and Avkhimenko, 1974).

Nemagon and EDB are also known mammalian carcinogens (Olson et al., 1973), while several organobromine compounds have been found mutagenic:

(1) 1,2-EDB, 1,1-EDB, 1-bromo-2-chloroethane, 1,5-dibromopentane, 1,2-dibromo-2-methylpropane, and 1,1,2,2-tetrabromopentane in *E. coli* and *S. typhimurium* (Brem et al., 1974).

(2) 1,2-EDB and 1,2-dibromopropane in *Drosophila melanogaster* (Vogel and Chandler, 1974).

Generally, organobromo compounds have greater mutagenic and DNA-modifying activity than their chloro analogs (e.g., EDB > EDC). In addition, the biological activity is enhanced when more than one bromine is attached to the same carbon atom (1,1-EDB > 1,2-EDB). When the halogens are on different carbons, however, the distance between the halogens has no appreciable effect on the activity (Brem et al., 1974).

## Bromine Phytotoxicity and Other Problems in Arkansas

As noted previously, most domestically produced bromine is extracted from brines in the El Dorado-Magnolia area of Arkansas. Bromine released as a consequence of these production activities has had serious effects upon vegetation in the locale. The first noted manifestation of a problem was damage to coniferous trees near the bromine plants. Needle tip necrosis after 13- to 14-month and 1- to 2-month exposure times was very evident within a 3-mile radius of all bromine facilities sampled. At further distances of 3.5 to 12 miles, tip damage was sporadic, varying from tree to tree, and not evident on 1- to 2-month-exposure needles. The foliage burn and death of trees within 0.5 to 1 mile of each plant site was extreme. Conifers were decidedly more susceptible to the bromine emissions than were broadleaf trees, shrubs, and grasses. Chlorophyll (a and b) levels were greatly reduced in the conifer trees surrounding the bromine plants. This was taken as a strong indicator of extreme air pollution problems because chlorophyll does not reflect environmental problems until they become overwhelming (Gordon, 1976).

The evidence of vegetative damage prompted the initiation of air-monitoring activities in the locality. Preliminary results have shown the presence of several potentially dangerous organobromine compounds in the air near the bromine production sites.

## Bromine and Stratospheric Ozone

In the past few years, there has been increasing concern over the depletion of the earth's protective stratospheric ozone layer by various human activities. The reduction of stratospheric ozone could have severe adverse effects on climate, agriculture, and skin cancer rates. At the forefront of this area, recently, has been the theory that certain widely used chlorofluorocarbon aerosol propellants and refrigerants are transported into the stratosphere by atmospheric motions, where the chlorine atoms in the molecules are released by photolysis. The chlorine then acts, through a catalytic cycle, to destroy ozone molecules. It has also been recognized that, like chlorine, any bromine entering the stratosphere will also destroy ozone catalytically. Furthermore, the bromine cycle is believed to be more efficient in destroying ozone than is the chlorine cycle.

Many of the manmade bromine compounds do not appear to be of significance to stratospheric ozone because of properties or use patterns which would preclude their reaching the stratosphere. Others have been identified as potential problems, such as methyl bromide, for which Wolfsy et al. (1975) have cautioned against unconstrained growth in use. Still other compounds, now produced in too small a quantity to be a significant threat (for example, the fire-extinguishing agents bromotrifluoromethane and bromochlorodifluoromethane), have properties which clearly indicate that they could, if produced in larger amounts, be of serious concern.

## Bromine Compounds in Water

One of the potential growth areas for bromine is in the purification of drinking water. The switch from chlorine to a bromine or bromine chloride water sanitation system is not without possible health implications. Bunn et al. (1975) found that the addition of KBr to natural Missouri River water caused a substantial reduction in the chloroform concentration while increasing the levels of bromodichloromethane, dibromochloromethane, and bromoform found in the sample. As noted earlier in this report, brominated compounds generally display greater biological activity than their chlorinated analogs. In view of this, any purification technique which may increase the levels of brominated methanes in drinking water should be carefully evaluated before being allowed to come into operation.

Another aspect of this problem is the influence of man's other activities on the bromine levels found in natural surface waters. Bromine should be a conservative property of water (Skopintsev [1973] estimates bromine's half-life in the Black Sea to be 1,800 years) and will not be efficiently removed via biological or sedimentation processes. Tiffany et al. (1969) report that the bromine concentration in the Great Lakes has increased steadily with time as a consequence of both pollution and natural processes. The major pollution sources are auto emissions and industrial effluents.

A final problem with bromine concerns the naturally occurring levels of bromine found in well waters. Fried et al. (1975) speculate that some instances of bromism in rural areas are actually due to bromide contamination of drinking water. They cite the occurrence of 0.08% bromine in a soft-water source in Kansas as an extreme example of what may be a real, though unrecognized, problem.

## Summary and Conclusions

Bromine is found naturally in the environment at relatively low levels. As a consequence of human activities, however, the concentration of bromine found in the ambient environment has greatly increased. Most of this rise is due to bromine released to the atmosphere following the combustion of leaded gasoline, although other sources (industrial processes, wastes, etc.) have contributed as well.

The long-term health and environmental implications of elevated bromine levels, while not known with certainty, are of some concern. The carcinogenic and mutagenic activity associated with organobromine compounds represents the most immediately evident of these concerns. The significance of the other problem areas outlined in this paper is more difficult to appreciate. Bromism, for instance, may occur as the direct result of increased exposure to $Br^-$ in air and, particularly, water. Current exposure data, however, are not available to assist in the delineation of the problem. This, in combination with the subtle nature of bromism, keeps the problem vague. The bromine-stratospheric ozone situation, bromine as a water sanitizer, and the extent of the Arkansas problem are also poorly defined. The information gaps preclude any considered assessment of the significance of each at this time.

Presently, bromine use and consumption patterns are changing and thereby altering the nature of the anthropogenic source. The declining demand for EDB is forcing the bromine industry to find new outlets for the anticipated bromine glut. Fire- and flame-retardant materials are currently seen as one of the growing consumptive uses of bromine; however, other product types must be developed before the bromine market will firm up. The anticipation is that TSCA will play a large role in decisions as to the acceptability of these new products and uses.

## REFERENCES

Amir, D. Sites of spermicidal action of ethylene dibromide in bulls. J. Reprod. Fert. 35(3):519-525, 1973.

Brem, H., A. B. Stein, and H. S. Rosenkranz. The mutagenicity and DNA-modifying effect of haloalkanes. Cancer Res. 34:2576-2579, 1974.

Bunn, William E., Bernard B. Haas, Edward R. Deane, and Robert D. Kleopfer. Formation of trichloromethanes by chlorination of surface water. Environ. Lett. 10(3):205-213, 1975.

Campbell, J. D. Bromide intoxication. South. Med. J. 42:697-673, 1949.

Chemical Economics Handbook (CEH). Menlo Park, Calif., Stanford Research Institute. 1975, 1976.

Edwards, K. et al. Studies with alkylating agents. II. A chemical interpretation through metabolic studies of the antifertility effects of ethylene dimethane-sulfonate and ethylene dibromide. Biochem. Pharmacol. 19:1783, 1970.

Faidysh, E. V., and M. G. Avkhimenko. Effect of the nematocide nemagon on the reproductive function of an organism. Tr.-Uzb. Naucho-Issled. Inst. Sanit., Gig. Profzabol. 8:42-43, 1974. (Abstract)

Fried, Frederick E., and Parviz Malek-Ahmadi. Bromism: Recent perspectives. South. Med. J. 68(2):220-222, 1975.

Gleason, M. N., R. E. Gosselin, H. C. Hodge, and R. P. Smith. Clinical Toxicology of Commerical Products, 3rd ed. Baltimore, The Williams and Wilkins Co. 1969.

Gordon, C. C. Report on coniferous vegetation collected in Union County and Magnolia area, Arkansas. Unpublished report, July 1976.

Neiswander, A. C. Bromide poisoning. J. Am. Inst. Homeopathy 51:104-105, 1958.

Olson, W. A. et al. Induction of stomach cancer in rats and mice with halogenated aliphatic fumigants. J. Natl. Cancer Inst. 51(6):1993-1995, 1973.

Opitz, J. M., F. R. Grosse, and B. Haneberg. Congenital effect of bromism. Lancet 1(7741):91-92, 1972.

Sax, N. Irving. Dangerous Properties of Industrial Materials, 3rd ed. New York, Van Nostrand Reinhold Co. 1968.

Shapovalov, Y. D. Effect of elemental bromine and its compounds on the organism of workers. Vrach. Pelo 12:110-115, 1974. (Abstract)

Skopintsev, B. A. Average residence times of some elements in Black Sea water. Okeanologiya 13(6):1015-1019, 1973. (Abstract)

Stenger, V. A. Bromine. In Kirk-Othmer Encyclopedia of Chemical Technology, 2nd ed., vol. 3. 1964. p. 750-766.

Tiffany, Mary A., John W. Winchester, and Ronald H. Loucks. Natural and pollution sources of iodine, bromine and chlorine 1329, 1969.

Vogel, E., and J. L. R. Chandler. Mutagenicity testing of cyclamate and some pesticides in Drosophila melanogaster. Experimentia 30:621-623, 1974.

Wolfsy, Steven C., Michael B. McElroy, and Yuk Ling Yung. The chemistry of atmospheric bromine. Geophys. Res. Lett. 2(6):215-218, 1975.

Woodbury, D. M. Antiepileptic drugs: Bromides. In Antiepileptic Drugs. 1972. pp. 519-527.

# CHEMICAL HAZARD INFORMATION PROFILE

## Carbon Black

Date of report: August 1, 1976

This chemical was chosen for study because of its high production volume and its potential for adsorbing carcinogenic substances.

It is recommended that OTS update its literature search on carbon black, since this report was written some time ago. Carbon black is recommended for testing consideration because of the potential for widespread exposure to the PNAs present in carbon black.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

## Chemical Identity

Carbon black, the darkest and most finely divided substance known to man, is produced in large quantities and is used primarily as a reinforcing agent in the manufacture of rubber tires. While there appears to be no significant direct toxic effect of carbon black itself, there is a question of a hazard due to carcinogenic polycyclic aromatic hydrocarbons known to be adsorbed on some types of carbon black. The bioavailability of these adsorbed carcinogens under conditions of human exposure has not yet been adequately demonstrated, and therefore the human health hazard of carbon black is equivocal. Pollution from the production of carbon black is minimal, but through tire wear and disposal of old tires, carbon black can reach the general environment.

Carbon black is elemental carbon in particulate form. The individual carbon atoms are arranged in platelets measuring 12 x 24 angstroms (A), similar to graphite, but with the platelets stacked only roughly parallel to one another. There are four basic types of carbon black, generally classified according to the production processes used for their manufacture. The four major processes for carbon black production are the furnace (either oil or gas) process, the thermal process, the channel process, and the lamp process. Acetylene black is a special type of thermal black utilizing acetylene as the make gas.

The properties of carbon blacks are a function of the process used to make the material. Table 1 presents the ranges of properties for different kinds of carbon blacks. Distinctions between types of various carbon blacks are based on particle size, surface area, chemical composition of the surface, and the extent of particle-to-particle association.

Under an electron microscope, all types of carbon blacks appear to be spherical particles that are more or less associated into loose chains. This tendency to form chains is known as chain structure, or simply structure, and has been correlated to compressibility and oil absorption. Structure has an important effect on the properties that carbon blacks give to rubber formulations, affecting ease of extrusion, electrical conductivity, and elastic modulus. Generally, channel and thermal blacks are low in structure, lampblacks are high, and furnace blacks exhibit a wide range, depending on production procedures.

Channel carbon black particles range from 100-400 A, thermal blacks from 1,400 to over 4,000 A, lampblacks from 600-4,000 A, and the versatile furnace blacks from 180-800 A. Surface area values, expressed in $m^2/g$ of black, are usually determined in one of two ways. One method of calculation is by measurement of average particle diameter; however, errors are introduced into this method through decreases in surface area in aggregated particles. A more convenient method is determining $N_2$ adsorption at -193°C, where the quantity of $N_2$ corresponding to monolayer coverage can be graphically determined. This method gives external and internal surface area, and in porous blacks values two or three times those obtained through calculations from measured diameters may result. Highly porous blacks are those with a more irregularly arranged crystalline structure.

When first collected, the bulk density of carbon black is about 3-10 $lb/ft^3$. Removal of occluded air raises this to 6-15 $lb/ft^3$. When pelletized for shipping, the bulk density of carbon black ranges from 20-30 $lb/ft^3$. More precise values for specific density, obtained through helium displacement methods, give values of about 1.86 $g/cm^3$.

Table 1. Typical Analytical Properties for Selected Carbon Blacks

| Type and process | Average particle diameter (A) | Surface area ($N_2$ adsorption, ($m^2/g$) | Volatile matter content (%) | pH | Benzene extract (%) | Oil adsorption ($cm^3/g$) |
|---|---|---|---|---|---|---|
| Channel process gas blacks | | | | | | |
| High-color channel | 90-140 | 1000-400 | 16-5 | 3-4 | None | 2-4 |
| Medium-color channel | 150-170 | 550-320 | 10-5 | 4-5 | None | 1.5 |
| Regular-color channel | 220-290 | 140-100 | 5 | 5 | None | 1.1 |
| Easy-processing channel | 300-290 | 100 | 5 | 5 | None | 1.0 |
| Medium-processing channel | 250-280 | 110-120 | 5 | 5 | None | 1.0 |
| Medium-flow channel | 230-250 | 200-210 | 7-8 | 4 | None | 1.1 |
| Long-flow channel | 220-280 | 300-360 | 12 | 3.5 | None | 1.2 |
| Furnace process gas blacks | | | | | | |
| Fine furnace | 400-500 | 40-50 | 1.0 | 8-9 | 0.05 | 0.9-1.1 |
| High-modulus furnace | 600 | 30-40 | 1.0 | 8-9 | 0.10 | 0.85 |
| Semireinforcing furnace | 600-800 | 25-30 | 1.0 | 8-9 | 0.15 | 0.7-0.8 |
| Furnace process oil blacks | | | | | | |
| Superabrasion furnace | 180-220 | 90-125 | 1.0 | 8-9 | 0.05 | 1.5 |
| Intermediate superabrasion furnace | 230-250 | 115 | 1.0 | 8-9 | 0.05 | 1.3 |
| Intermediate superabrasion furnace, low structure | 200-230 | 110-130 | 1.5 | 8-9 | 0.05-0.1 | 0.8-0.9 |
| Intermediate superabrasion furnace, high structure | 225 | 110-130 | 1.5 | 8-9 | 0.05 | 1.4-1.6 |
| High-abrasion furnace | 260-280 | 74-100 | 1.5 | 8-9 | 0.05 | 1.15 |
| High-abrasion furnace, low structure | 250-265 | 85-110 | 1.5 | 8-9 | 0.05 | 0.7-0.8 |
| High-abrasion furnace, high structure | 220-250 | 80 | 1.5 | 8-9 | 0.05 | 1.4-1.6 |
| Fast-extruding furnace | 400-450 | 40-45 | 1.0 | 9 | 0.05 | 1.3-1.4 |
| General-purpose furnace | 500-550 | 25-30 | 1.0 | 9 | 0.05 | 0.9 |
| Conductive furnace | 210-290 | 125-200 | 1.5-2.0 | 8-9 | 0.06 | 1.3 |
| Thermal process gas blacks | | | | | | |
| Fine thermal | 1,800 | 13 | 0.05 | 9 | 1.75 | 0.3-0.5 |
| Medium thermal | 4,700 | 7 | 0.05 | 8 | 0.3 | 0.3-0.5 |
| Other processes | | | | | | |
| Lampblack | 650-1,000 | 20-40 | 0.4-9 | 3-7 | 0.01-0.5 | 1.3-2 |
| Acetylene black Shawinigan | 420 | 64 | 0.3 | 5-7 | 0.1 | 3.4 |

Carbon black is 90-99% pure carbon. Oxygen and hydrogen are present primarily as complexes with surface carbon resulting from interactions after the black has been formed. The carbon content of carbon blacks varies (% by weight) from 88.4 for high-color channel to 99.5 for thermal acetylene. The oxygen content varies inversely, with 11.2 for high-color channel to no measurable amount for thermal acetylene. Also, the volatile content varies inversely with 18 for high-color channel and 0.06 for thermal acetylene (Kirk-Othmer, 1964). Some such complexes are hydroxyl, carbonyl, and carbonic acid groups, some aromatic hydrogen, lactones, and heterocyclic ethers. Many carbon blacks adsorb polycyclic aromatic hydrocarbons (PAHs) during production; PAHs that have been identified include benzopyrene, naphthalene, acenaphthylene, phenanthrene, fluoranthrene, pyrene, cyclopenta-pyrene, phenalenone, benzperylene, anthanthrene, and coronene. PAHs comprise what is often referred to as the benzene extractable content of carbon black. Other contaminants include 0.01-0.2% sulfur from that present in the raw material and a few tenths of a percent of ash from the water used to quench the hot black in manufacture. The volatile content of carbon black is the percent weight loss after heating to 927°C. This is mostly carbon monoxide or carbon dioxide, and is generally between 1 and 2%, though in some channel blacks this may be up to 18%. The chemical properties and reactions of carbon black resemble those of polynuclear aromatic compounds, and most blacks exhibit a typical aromatic basicity, with normal pH values ranging from 8-10. A high proportion of surface oxygen groups tends to lower the pH, correlating nicely with an increased volatile content.

## Production and Use

All types of carbon blacks are produced by thermal decomposition of hydrocarbons, either through partial burning or by straight heating. High temperatures that promote uniform conditions for rapid heat transfer, rapid production of particles, proper dilution of starting material, and protection from oxidation are necessary for production of small and uniform particle size. Lampblack is produced by burning petroleum oils and coal tar by-products in shallow open pans with a restricted air supply. In the channel process, natural gas is burned in many small fan-shaped flames just below continuously moving channel irons. Insufficient air for complete combustion is provided, and carbon black forms in the flame and is deposited by impingement on the channel. Stationary scraper blades remove the black from the channels. About 5% of the carbon in the gas is recovered as black, but new techniques of enriching the gas with oil are being used because of the rising price of natural gas.

Thermal blacks are produced by the thermal decomposition of natural gas in the absence of air. Unlike all the other methods of carbon black production, the thermal process is cyclic rather than continuous in operation. The generator, which is a large furnace filled with a checkerwork of silica brick, is heated to 2,400-2,800°C by complete combustion of natural gas and air. When the desired temperature is obtained, the air is cut off and natural gas is admitted for the decomposition stage. The heat from the brickwork cracks the gas to elemental carbon and hydrogen gas. When the brick is too cool for further cracking, the gas is cut off and the carbon smoke is flushed from the generators. The cycle then repeats, with reheating of the checkerbrick by combustion of gas and the hydrogen produced in the decomposition cycle. About 40-50% of the carbon in the fuel is recovered. The particle size can be controlled somewhat by diluting the natural gas with recirculated resultant gas, which allows smaller carbon particles to form in the more dilute atmosphere.

The furnace process, which now dominates the carbon black industry, is similar to the channel and lamp processes in that it also involves incomplete combustion of hydrocarbons, but in the furnace process this takes place in a large furnace with a single flame utilizing large volumes of hydrocarbons and air. In the gas furnace process, air and natural gas are mixed and ignited in the ratios required for properly incomplete combustion. Adjustment of air/gas ratio, flow, and turbulence allows the characteristics and yield of the black to be regulated. For larger size gas furnace blacks, the yield may be between 25 and 30%, while the production of small particles recovers only about 10-15% of the total carbon. In the oil furnace process, air and natural gas are burned completely in a process separate from the decomposition step. The oil, typically a highly aromatized petroleum oil, is atomized and injected into the heat of the swirling zone of complete combustion, where it is decomposed to a fine carbon smoke and hydrogen gas. Here again, the qualities of the black can be adjusted, but over a very wide range in this case, by changing ratios in the oil/air/gas mixture and in furnace and injector design. Yields in this process are high, typically around 55%, and will vary between 35 and 65%.

After the thermal decomposition step has taken place, the black must be collected and packaged for further use. In the lamp process, most of the black is collected through precipitation in large settling chambers. Channel black is primarily collected directly by scraping from the channels themselves. Neither of these measures is completely efficient, and collecting devices such as cyclones, precipitators, and filters are employed to varying degrees. The off-gas from the thermal and furnace processes, which contains the suspended carbon black particles, must first be cooled to about 500°C in a spray tower. Following this step, collection devices such as electrostatic precipitators, wet scrubbers, cyclones, and bag filters are used to collect the black. In older plants, electrostatic precipitators and cyclones were widely utilized, but due to economic and versatility problems with precipitators as well as greatly improved designs for bag filters, the presently preferred set-up for collection systems consists of an agglomerating device or cyclone followed by bag filters. This sequence of collectors will remove over 99% of the carbon black from the combustion gases.

The recent trends in carbon black production have been to shift emphasis away from channel black, which historically played a large role, to furnace black due to advances in furnace technology which allow a wide range of blacks with properties similar to channel blacks to be produced. Furnace black now makes up almost 92% of U.S. production, thermal black about 8%, with channel and lampblack together comprising less than 0.1% of the total output.

Production data for carbon blacks are shown in Tables 3 and 4.

Carbon black consumption data are shown in Table 5. About 93% of the carbon black produced in the United States is consumed by the rubber industry; of this, 90% is used as a reinforcing agent in rubber tires. About 6-7 lb of carbon black goes into each tire, the primary effect of which is to extend the abrasion resistance and thus the useful life of the tire. The type of carbon black used and the amount added also affect the electrical conductance, heat buildup, resilience, flex resistance, and processing characteristics of the rubber. Besides tire treads, carbon black is also added to rubber belts, hoses, wire insulation, flooring, motor mounts, and rubber gaskets. All kinds of carbon black are utilized for these applications, depending on the specific characteristics required.

The second largest consumer of carbon black is the ink industry, especially for use in newsprint. Furnace black has largely replaced channel black for this application. Channel and furnace blacks are also used in book, letterpress, lithographic, gravure, carbon paper, and typewriter ribbon inks. Other pigment applications for various grades of carbon black include uses in paints, lacquers, enamels, coloring plastics, black paper, nylon and other fibers, tinting dispersions, and as a toner in electrostatic copying machines.

Other useful applications of carbon black are as an antistatic agent in phonograph records, to prevent photo and thermal oxidation in polyolefins, in black tape for wrapping high-voltage transmission cables, in dry-cell batteries (acetylene black), for high-temperature insulation, and in carbon electrodes (lampblack).

Table 3. Carbon Black Production by Process (millions of lbs)

| Year | Furnace | Thermal | Channel | Total |
|---|---|---|---|---|
| 1960 | 1,612 | 149 | 292 | 2,054 |
| 1961 | 1,567 | 145 | 262 | 1,980 |
| 1962 | 1,677 | 172 | 207 | 2,056 |
| 1963 | 1,686 | 194 | 179 | 2,059 |
| 1964 | 1,821 | 232 | 170 | 2,223 |
| 1965 | 1,933 | 272 | 148 | 2,354 |
| 1966 | 2,142 | 276 | 153 | 2,572 |
| 1967 | 2,028 | 306 | 149 | 2,484 |
| 1968 | 2,364 | 305 | 143 | 2,812 |
| 1969 | 2,505 | 326 | 132 | 2,963 |
| 1970 | 2,506 | 312 | 114 | 2,931 |
| 1971 | 2,629 | 342 | 46 | 3,017 |
| 1972 | 2,930 | 249 | 22 | 3,201 |
| 1973 | 3,170 | 316 | 14 | 3,500 |
| 1974 | 3,116 | 274 | -- | 3,390 |

Source: SRI, 1976

Table 4. Carbon Black Production by Raw Materials (millions of lbs)

| Year | From natural gas | From liquid hydrocarbons |
|---|---|---|
| 1960 | 638 | 1,415 |
| 1961 | 598 | 1,381 |
| 1962 | 537 | 1,520 |
| 1963 | 543 | 1,516 |
| 1964 | 574 | 1,649 |
| 1965 | 593 | 1,761 |
| 1966 | 524 | 2,048 |
| 1967 | 466 | 2,018 |
| 1968 | 455 | 2,357 |
| 1969 | 456 | 2,507 |
| 1970 | 381 | 2,550 |
| 1971 | 322 | 2,695 |
| 1972 | 271 | 2,930 |
| 1973 | 246 | 3,254 |
| 1974 | -- | 3,207 |

Source: SRI, 1976.

Table 5. Carbon Black Consumption by End Use (millions of lbs)

| Year | Elastomers | Printing inks | Paint |
|---|---|---|---|
| 1960 | 1,363 | 48 | 12 |
| 1961 | 1,383 | 43 | 15 |
| 1962 | 1,551 | 41 | 16 |
| 1963 | 1,630 | 46 | 13 |
| 1964 | 1,789 | 46 | 18 |
| 1965 | 1,946 | 54 | 11 |
| 1966 | 2,131 | 64 | 12 |
| 1967 | 2,072 | 64 | 13 |
| 1968 | 2,446 | 68 | 13 |
| 1969 | 2,616 | 73 | 18 |
| 1970 | 2,486 | 73 | 15 |
| 1971 | 2,678 | 75 | 19 |
| 1972 | 2,954 | 82 | 21 |
| 1973 | 3,115 | 84 | 22 |
| 1974 | 2,925 | 83 | 19 |

Source: SRI, 1976.

The Food and Drug Administration (FDA) has lifted its conditional approval of channel black for use as a food color additive for licorice and jellybeans. This was done because the industry could not meet the conditions of approval, which were requirements for specifications to differentiate channel from other types of black and for analytical methods to detect PAHs in channel black at a level of 2 ppb. The only other black approved for food-associated use by the FDA is furnace black, which may be incorporated at less than 10 ppb into rubber articles for repeated use in food preparation.

## Health Aspects

Much of the original toxicity testing of carbon black was carried out by Carl Nau, Jack Neal, and Vernie Stembridge in the late 1950's, and their work is still the most complete body of information on carbon black available. Their work, like most of the available literature, concentrates on the carcinogenic polycyclic aromatic hydrocarbons, especially benz(a)pyrene, that are known to be adsorbed on several types of black. Channel blacks are low in this benzene extractable content, thermal and lampblacks are high, and furnace blacks fall into an intermediate category. Blacks with average diameters under 300 A usually contain no PAHs, while those over 500 A contain a variety (Steiner, 1954).

Male mice fed a diet containing 10% furnace black for 72 weeks showed no gross changes from controls, while alive or when autopsied, whereas animals given the benzene extract of this black incorporated into the diet developed a significant number of tumors in the gastrointestinal tract (Nau et al., 1958). In another study, various air pollutant particulates including carbon blacks were incorporated into the diet of 83 mice, of which 8 developed gastric tumors (Neal and Rigdon, 1969).

Nau and his associates (1958) painted the skins of mice, rabbits, and monkeys with a 20% suspension of carbon black in water, cottonseed oil, or mineral oil three times per week for a year and observed no changes from controls, while the benzene eluted component of the same black induced skin malignancies in all three species.

In another set of experiments, 300-mg pellets of carbon black from which benz(a)pyrene could be eluted were injected subcutaneously into mice and induced two sarcomas in 50 mice. A black which did not yield any PAHs on benzene elution was able to induce one sarcoma in 50 mice when similarly injected, although the same carbon black with 0.09 mg of benz(a)pyrene added failed to produce any sarcomas. The benz(a)pyrene-containing carbon black induced 18 tumors in 50 mice when 300 mg was injected subcutaneously with tricarprylin, an oily solvent (Steiner, 1954).

Pylev (1970) reintroduced benzopyrene into channel and thermal blacks from which the absorbed compounds had been "burned out" by heating at 900°C. These carbon blacks, containing 0.01 mg of benzopyrene per 1.0 mg of black, were given in 60-mg doses to rats by intratracheal intubation. The channel black thus administered induced tumors in 40.4% of 52 rats in 16 months, and the thermal black induced lung tumors in 24% of 50 rats in 10 months.

Nau and his associates (1962) carried out a fairly extensive series of inhalation studies on carbon black. Mice (for their lifespan), guinea pigs, and monkeys (up to 13,000 total hours) were exposed to 1.6 mg/m$^3$ of various types of furnace blacks for 7 hr per day, 5 days per week. No tumors were induced in any of the animals studied. In histological studies, carbon black was found scattered through lung tissue both free-lying and inside macrophages (scavenger cells). In mice, the black was diffuse and finely distributed, while monkeys progressively developed diffusely distributed areas of nodularity where the black was concentrated. The walls of the alveoli tended to be thickened, and in some animals there was some minimal fibrosis which did not progress with continued exposure. Carbon black was observed to infiltrate the pulmonary lymph nodes, and was also present in the liver, spleen, and kidneys of exposed animals but with no apparent effect. Inhalation of furnace black did produce an increase in the heart weight/body weight and lung weight/body weight ratios in mice. Monkeys inhaling furnace carbon black showed electrocardiographic changes indicative of atrial and right ventricular strain after 2,500 hr of exposure. Inhalation by monkeys of a thermal black resulted in right and left ventricular and septal hypertrophy. Tests of pulmonary function in mice exposed to thermal blacks and monkeys exposed to furnace blacks indicated no changes in air flow or gas exchange.

The key question in the problem of carbon black carcinogenicity appears to be the degree to which the adsorbed carcinogenic PAHs are able to be removed from the carbon black under conditions of human exposure. Human blood plasma, artificial gastric juice, or artificial intestinal juice did not elute any PAHs from channel or furnace blacks after 120.5 hr at 28°C and 60 hr at 37°C with intermittent shaking. Cottonseed oil, aqueous citric acid (pH 3.85), 3% aqueous acetic acid, 3% aqueous sodium bicarbonate, 3% aqueous sodium chloride, and whole milk did not remove any PAHs from carbon blacks incorporated into a commercial rubber fabrication after 7 days at 138°F (Neal et al., 1962). Alveolar and peritoneal macrophages are able *in vitro* to elute benzopyrene from carbon blacks to which it has been added (Tomingas et al., 1971).

One segment of the carbon black industry has been examined for overall mortality rate and for specific mortality due to cardiovascular disease and cancer. The overall annual mortality for carbon black workers was low over the 17.5-year period (1939-56) examined: 3 deaths per 1,000 among carbon black workers versus an expected annual mortality of 4.9 per 1,000. Death due to cardiovascular diseases was less than expectancy, as was death from cancer, at 1.2 rather than 1.46 deaths per 1,000 (Ingalls and Risquez-Iribarren, 1961). This last statistic was not broken down for types of cancers reported and may thus be misleading; two of the five cancerous lesions reported in carbon black workers were melanocarcinomas of the skin, of a type conceivably traceable to carbon black.

Studies have been made of pulmonary function in workers at a carbon black plant (type unspecified) exposed to concentrations of carbon dust in the air averaging less than 10 mg/m$^3$. The parameters of function analyzed were forced vital capacity (FVC) and forced expiratory volume in 1 sec (FEV$_1$). The average annual decline in FVC for the carbon black workers was more than four times that expected for a normal male population, while the average annual decline in FEV$_1$ was almost three times the predicted value over the 7 years (1964-71) of the survey. Radiological lung changes consisting of discrete reticular and finely nodular fibrosis were detected in 6 out of the 35 workers (17.1%) examined. The average exposure of these 6 was 15.6 years (Valic et al., 1975).

The results outlined in the above presentation can scarcely be called conclusive in any direction. It appears that carbon blacks naturally containing adsorbed PAHs do not produce tumors, while both positive and negative reports on blacks with added benz(a)pyrene have been presented. It seems possible that under conditions where a proper lipid solvent is present, such as on the skin or in certain pathogenic lungs, the carcinogenic PAHs adsorbed on carbon black may be eluted and thus become available; however, this question cannot be resolved from the available scientific literature.

## Environmental Aspects

The carbon black industry is interesting from the pollution control aspect in that the objective is to produce large quantities of dense carbon smoke that would under any other circumstances be regarded as highly undesirable by-products. But because this highly divided particulate matter is the product of the carbon black industry, careful and generally highly efficient methods have been developed for complete collection for purely economic reasons. In the thermal and furnace process plants, systems of electrostatic precipitators, cyclones, and bag filters will collect over 99% of the black. The general procedure is to burn the waste gases from the furnace process after the black has been removed; the major pollutants after this has been completed are carbon dioxide and, if a sulfur-containing fuel had been used, sulfur dioxide. The off-gas from the thermal process is contained and utilized as a fuel due to its caloric value from the high content of hydrogen gas. In the channel process, the carbon is collected by impingement on long-channel irons. Much of the carbon does not impinge in this way, however, and can escape to the atmosphere.

Channel plants are notorious for the great volumes of black smoke which they produce and which can be seen over 30 miles away. Any attempt to regulate the escape of the gases from the burning houses would require controlling the ventilation to an extent where the production processes themselves would be irreversibly impaired. Only one channel black plant is in operation in the United States, built near a natural gas field in remote western Texas. Therefore, complaints of pollution from this source seldom arise. Since the channel process has been largely superseded by new furnace technology and no new channel black plants have been built in the United States since 1950, this would not seem to present any major problems for the future.

Sources of carbon black to the atmosphere other than from production processes mainly arise through maintenance procedures, leaks in plant conveying systems, or loading and unloading operations. A plantwide vacuum system and good housekeeping procedures where all spillage is picked up and combusted or recycled can eliminate most problems from this source. Similar controls should be instituted where carbon black is handled in further processing (i.e., rubber plants).

The Effluent Guidelines Division of EPA has recommended criteria of no discharge of carbon black into wastewater from any type of carbon black plant. The basis for this decision lies in the fact that the lamp and channel processes are dry, with no use of water or entry of carbon black into the water. The thermal and furnace processes are designated as net water consumers, namely, at the stage where water is used to quench the hot black immediately after production. Any waters contaminated with black through cleanup or wet scrubbers later in the separation process could be recycled to the quenching step, and the black contained therein could be reintroduced into the separation process. The criterion of no discharge into wastewater seems to be achievable with little impact on the production cost of carbon black.

Since the bulk of the carbon black produced is utilized as a reinforcing agent for rubber tires, the ultimate disposal of carbon black into the environment comes through tire wear. Carbon black contaminated with rubber is thus lost in substantial quantities along the roadways, although it appears that most of these particles settle out within a few feet of the road, ultimately entering the soil or being washed into the waterways. There are no data on the action of carbon black in ecological media, but it would be expected to be inert under normal conditions, with little washout of any adsorbed chemicals.

Carbon black has some potential for human exposure. Individuals encountering the highest levels of carbon black will do so in an industrial environment, such as the carbon black, tire, or printing ink industries. However, a wider population may also be exposed to low levels of carbon black inhaled in minute quantities as a component of tire dust.

## REFERENCES

Allan, D. L. The prevention of atmospheric pollution in the carbon black industry. Chem. Ind., p. 1320-1324, 1955.

Drogin, I. Carbon black. Air Pollut. Control Assoc. 18(4):216-228, 1968.

Environmental Protection Agency. Carbon black manufacturing point source category. Interim final rule making. Fed. Reg. 41(97):20496-20504, 1976.

Ingalls, T. H., and R. Risquez-Iribarren. Periodic search for cancer in the carbon black industry. Arch. Environ. Health 2:429-433, 1961.

Kirk-Othmer Encyclopedia of Chemical Technology. New York, John Wiley and Sons. 1964.

Kirk-Othmer Encyclopedia of Chemical Technology. New York, John Wiley and Sons. 1965.

Nau, C. A., J. Neal, and V. Stembridge. Physiological effects of carbon black. I. Ingestion. AMA Arch. Ind. Health 17:21-28, 1958.

Nau, C. A., J. Neal, and V. Stembridge. Physiological effects of carbon black. II. Skin contact. AMA Arch. Ind. Health 18:511-520, 1958.

Nau, C. A., J. Neal, V. Stembridge, and R. N. Cooley. Physiological effects of carbon black. IV. Inhalation. Arch. Environ. Health 4(4):415-431, 1962.

Neal, J., and R. H. Rigdon. Stomach cancer and air pollution: An experimental study in a petrochemical area. Tex. Rep. Biol. Med. 27(3):787-793, 1969.

Neal, J., M. Thornton, and C. A. Nau. Polycyclic hydrocarbon elution from carbon black or rubber products. Arch. Environ. Health 4:598-606, 1962.

Pylev, L. N. Induction of experimental lung cancer by chemical substances. Oncology 2:441-446, 1970.

Stanford Research Institute. Chemical Economics Handbook. Menlo Park, Calif. 1976.

Steiner, P. E. The conditional biological activity of the carcinogens in carbon blacks, and its elimination. Cancer Res. 14:103-110, 1954.

Tomingas, R., H. U. Lange, E. G. Beck, N. Manojlovic, and W. Dehnen. The elution of benzo(a)pyrene adsorbed on particles by macrophages cultured in vitro. Zentralbl. Bakteriol. Parasitenkd. Infektionskr. Hyg. Erste. Abt. Orig. Reihe B Hyg. Praev. Med. 155(2): 148-158, 1971.

Valic, F., D. Beritic-Stahuljak, and B. Mark. A follow-up study of functional and radiological lung changes in carbon black exposure. Int. Arch. Arbeitsmed. 34:51-63, 1975.

# CHEMICAL HAZARD INFORMATION PROFILE

## Cutting Fluids

Date of report: May 1, 1977

These substances were chosen for study because of the demonstrated presence of nitrosodiethanolamine, a carcinogen, in certain synthetic cutting fluids.

No further work by this Office concerning occupational hazards appears necessary because a NIOSH Criteria Document on cutting fluids is in progress. It is recommended that this report be referred to the Office of Solid Waste for consideration of disposal problems. It appears that inadequate disposal methods represent the major source of nonoccupational exposure of cutting fluids.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

### Category Identity

Cutting fluids are liquids applied to a metal cutting tool to assist in the machining operation by washing away metal chips or serving as a coolant or lubricant. Many materials find common usage as cutting fluids: water solutions or emulsions of detergents and oils; minerals oils; fatty oils; chlorinated mineral oils; sulfurized mineral oils; and mixtures of the above (Condensed Chemical Dictionary, 1971).

The exact composition of commercially used cutting fluids is difficult to determine because of proprietary considerations and the common practice of additive incorporation at the place of use (e.g., the machine shop). Table 1 presents a breakdown of the most commonly encountered constituents of commercial cutting fluids.

### Health Aspects

Documented health problems associated with cutting fluids are related to occupational exposure. The nature and scope of the difficulties arising from environmental exposure to cutting fluid wastes is not well defined. The composition of those

Table 1. Composition of Commercial Cutting Fluids

| | | |
|---|---|---|
| (A) Synthetic cutting fluid or chemical coolant | | |
| 50-90% | (1) | Water |
| 1-10% | (2) | Rust inhibitors and detergents |
| | | (a) sodium nitrite |
| | | (b) di- and triethanoleamines |
| | | (c) potassium or sodium soaps |
| 25-50% | (3) | Lubricating agents |
| | | (a) polyether glycols |
| | | (b) alkyl-phenol-ethylene oxide condensation products |
| 0-1% | (4) | Bactericides |
| | | (a) chlorophenols |
| | | (b) organic mercurials |
| | | (c) iodine compounds |
| | | (d) formaldehyde releasers |
| | | (e) quaternary ammonium compounds |
| | | (f) hexachlorophene |
| Note: | | Synthetic cutting fluids are diluted (20-150:1) with water prior to use. |
| (B) Soluble or semisynthetic cutting fluids | | |
| 60-90% | (1) | Mineral oils |
| 1-5% | (2) | Water |
| 5-30% | (3) | Emulsifiers |
| | | (a) sodium and amine soaps |
| | | (b) sodium sulfonates, naphthenates, rosinates |
| 1-20% | (4) | Coupling agents |
| | | (a) alcohols |
| | | (b) glycol ethers |
| | | (c) glycols |
| 1-10% | (5) | Rust inhibitors |
| | | (a) amines |
| | | (b) sodium nitrite |
| | | (c) fatty oils |
| | | (d) sulfurized fatty oils |
| 0-10% | (6) | Bactericides (as above) |
| Note: | | Soluble cutting fluids are diluted with water prior to use. |
| (C) Insoluble or straight oils | | |
| 80-100% | (1) | Mineral oils (including sulfurized mineral oils) |
| 1-40% | (2) | Fatty oils (including sulfurized fatty oils) |
| 0-10% | (3) | Sulfur (combined and suspended) |
| 0-10% | (4) | Chlorine |
| | | (a) chlorinated paraffins; rarely chlorinated aromatics |
| 0-1% | (5) | Phosphorus |
| | | (a) organic phosphates and phosphites |

Source: Adapted from Gleason et al., 1969.

cutting oil effluents reaching a drinking water source is also obscure. Large users of cutting fluids, however, are more likely to have pollution restraints on their effluent than the relatively small-volume users, who may merely pour their spent fluids down a drain or onto the ground.

## Known Occupational Hazards

The problems associated with occupational exposure are many: eye irritation, pneumonitis, allergic skin sensitization, and acne and folliculitis which can lead to keratosis and hyperkeratosis, ultimately resulting in malignant dyskeratosis and squamous cell carcinoma if exposure continues (Seba, 1976).

Finklea (1976) reports that there are over 1,000 domestic producers and that in excess of 780,000 people are occupationally exposed to cutting fluids in the United States.

## Diethanolnitrosamine

Zingmark and Rappe (1976) first reported the formation of diethanolnitrosamine in a grinding fluid under simulated gastric conditions. Development of a chemiluminescent detector sensitive to the N-nitroso group has greatly increased the capacity for rapid detection of nitrosamines (although problems with the method remain). Using this instrument, Fan et al. (1977) reported concentrations of diethanolnitrosamine in commercial cutting fluids ranging from 0.02 to 2.99% (eight reported samples). Concern has arisen that the entry of appreciable quantities of this nitrosamine into a drinking water source may create a health problem.

Druckrey et al. (1967) reported that diethanolnitrosamine was a liver carcinogen in rats. A determination of the acute toxicity of diethanolnitrosamine showed it to have no lethal effects despite a large dose (7.5 g/kg). An initial long-term (feeding?) study established that the compound could induce liver cancer with an average daily dose of 1 g/kg (total dose, 300 g/kg). This study was repeated at a lower average daily dose level of 0.6 g/kg until one-half of the previous total dose was administered (total of 150 g/kg over 240 days). Following the cessation of treatment, all rats from the initial population of 16 died with liver cancer. Four of the 16 also had kidney adenomas. (No information was reported as to the fate of any controls.) The authors concluded that diethanolnitrosamine was an active carcinogen on the basis of the short induction period and the subsequent rapid development of tumors. They added, however, that the required active dose is at least 200 times greater than that with diethylnitrosamine (one of the most potent carcinogenic nitrosamines). The replacement of the diethylamine group with the diethanolamine function apparently weakened the carcinogenic activity but did not alter the organ specificity.

### Other Problems

Several additional components of cutting fluid formulations have potential for causing problems in the health area. These have been more or less summarized in the next section.

## Environmental Aspects

### Methods of Disposal

Many synthetic cutting fluids can be successfully biodegraded prior to disposal. This is based upon the relative ease with which long-chain fatty acids can be broken down into shorter chained fatty acids, thus reducing the "oily" character of the spent cutting fluid. Oil-base cutting fluids present a special problem because of the low allowable concentration of oil in wastewater. Biological degradation of hydrocarbons proceeds slowly, and therefore it is a common practice to subject spent cutting oils to physicochemical separation procedures. A process such as this attempts to separate the oil and water phases such that each can be dealt with individually. The aqueous phase often retains some oil, however, and must undergo additional treatment prior to disposal. The final disposal method is incineration of either the separated oil or the untreated cutting fluid. In the latter case, water is driven off as steam and the recovered oil is used to fuel the unit. This method solves the water pollution problem but is somewhat costly and may create an air problem (Bennett, 1973; Bouveng et al., 1972).

### Cutting Oil Components

Metals. Spent cutting fluids may contain significant concentrations of metal salts which can adversely affect the efficiency of sewage disposal plants. Metallic ions may also cause problems if they accumulate to levels higher than the environment can tolerate (Bennett, 1973).

Rust inhibitors. Cutting fluids contain significant amounts of rust inhibitors such as sodium, potassium, or lithium nitrites in their formulations. At low environmental concentrations, nitrites can be used as an energy source by microorganisms, while high levels can reduce the activity of sewage bacteria (Bennett, 1973).

Phosphates. Some metalworking fluids contain high concentrations of phosphates which are implicated in excessive algal growth and eutrophication problems (Bennett, 1973).

Others. Both hydraulic fluids and cutting fluids may contain polychlorinated biphenyls (PCBs), though their use is currently being phased out. Boron compounds are being included in some cutting fluid formulations at a time when the boron levels in rivers are increasing. Boron is difficult to remove by conventional waste treatment methods, and at high concentrations (over 1,000 ppm) it can interfere with the efficiency of disposal plants. Some newly developed, more exotic cutting fluids contain fluorides, iodides, and cadmium salts. These, however, are apparently rather low-volume products at this time.

An additional difficulty is the presence of biocides in cutting oil formulations. While the biocide concentrations are low (initially and especially after dilution), the tremendous volume of spent cutting fluids generated domestically can add a sizable environmental burden, especially in localized heavy-use areas. Another aspect is the apparently common practice of adding additional amounts of biocides to cutting fluid products at user sites to "ensure" effective microbial control (Bennett, 1973).

### Nitrosamines

Diethanolnitrosamine has been identified as a contaminant of several commercial cutting fluids. Fan et al. (1977) reported diethanolnitrosamine concentrations as high as 2.99% in an undiluted, commercially available virgin cutting fluid. The authors predicted that most cutting fluids containing di- or triethanolamines and nitrites as additives would also be contaminated with this nitrosamine. Health or environmental problems could arise following the disposition of nitrosamine-containing cutting fluids in a drinking water supply. None of the noted disposal methods (with the possible exception of incineration) are known to remove or reduce this potential problem with any certainty.

Druckrey et al. (1967) reported that diethanolnitrosamine is very soluble and quite stable in water under laboratory conditions (no indication as to the presence or absence of light). In natural waters, diethanolnitrosamine may undergo photolytic decomposition; however, there are no studies to indicate the half-life of diethanolnitrosamine under such conditions. Nevertheless, photolytic decomposition is effective only at the surface of waters, and if the nitrosamine is evenly dispersed throughout a reservoir, only a fraction would reside at the air/water interface.

It remains to be demonstrated that nitrosamines are present in user effluent and that the levels found in water subsequent to dilution are high enough to present a problem.

## REFERENCES

Bennett, E. O. The disposal of metal cutting fluids. Lubr. Eng. 29:300-307, 1973.

Bouveng, H. O. et al. Handling of spent oil-based products in the mechanical engineering industry. Pure Appl. Chem. 29(1-3):201-217, 1972.

Condensed Chemical Dictionary, 8th ed. New York, Van Nostrand Reinhold Co. 1971.

Druckrey, H. et al. Organotrophic carcinogenic effects of 65 different N-nitroso compounds on BD-rats. Krebsforsch. 69:103-201, 1967. (Translated by G. Semeniuk and C. Auer, EPA)

Fan, T. Y. et al. N-nitrosodiethanolamine in synthetic cutting fluids: A part-per-hundred impurity. Science 196:70-71, 1977.

Finklea, John F. Current Intelligence Bulletin: Nitrosamines in Cutting Fluids. October 6, 1976.

Gleason et al. Clinical Toxicology of Commercial Products, 3rd ed., Baltimore: The Williams and Wilkins Co., 1969.

Hart, Andrew W. Alkanolamines. In Kirk-Othmer Encyclopedia of Chemical Technology, 2nd ed., vol. I. 1963. p. 809-824.

Seba, Douglas B. Letter, April 20, 1976.

Zingmark, P. A., and C. Rappe. On the formation of N-nitrosodiethanolamine from a grinding fluid under simulated gastric conditions. Ambio 5:80, 1976.

## ADDENDUM

Chemical Week (1977) reported that diethanolnitrosamine has been identified by David Fine as a contaminant in several popular consumer products (shampoos, cosmetics, hand and body lotions). Lijinsky et al. (1972) demonstrated that triethanolamine is readily nitrosated when treated with sodium nitrite under acidic conditions. There is some likelihood that the problem of diethanolnitrosamine contamination may be common to other products.

During the course of this project, several additional, more wide-ranging questions came into view. Perhaps the most significant are the health and environmental consequences of the large-volume use and release of nitrates and nitrites. There is a multitude of problems associated with these materials aside from the possible nitrosamine implications.

### References

Chemical Week, March 30, 1977, p. 29.

Lijinsky, W. et al. J. Natl. Cancer Inst. 49:1239, 1972.

# CHEMICAL HAZARD INFORMATION PROFILE

## Cyclohexylamine

Date of report: October 21, 1977

This chemical was chosen for study because of reports of its toxicity in the scientific literature.

Since many other chemicals, especially other aliphatic amines, are also used as corrosion inhibitors and would therefore have similar exposure patterns, it is recommended that a contractor review the entire class of volatile corrosion inhibitors. This contractor report would serve as the basis for a Phase I document. The carcinogenic potential of these chemicals is the major impetus for further assessment.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

### Chemical Identity

Cyclohexylamine is a colorless liquid at room temperature and has an unpleasant fishy odor. It has a boiling point of 134.5°C and is a strong organic base ($pK_b = 3.3$). Cyclohexylamine forms an azeotrope with water (boiling point, 96.4°C) and is miscible with most organic solvents (Condensed Chemical Dictionary, 1977).

### Production and Use

The three processes used in the manufacture of cyclohexylamine (CHA) are the catalytic hydrogenation of aniline, ammonolysis of cyclohexyl chloride or cyclohexanol, and the reduction of nitrocyclohexane (Shreve, 1967). The first reaction is apparently the most common and involves the hydrogenation of aniline in the liquid phase at 135-137°C and 50-500 atmospheres of pressure in the presence of a catalyst. The CHA yield is approximately 80%

(Kouris and Northcott, 1967). The other reaction products are unchanged aniline and a high-boiling residue containing cyclohexylaniline and dicyclohexylamine (Merck Index, 1968).

CHA is a reactive primary amine and serves as an intermediate for a variety of derivatives. These compounds find use in numerous industries including chemical, paper, rubber, plastic, textile, pharmaceutical, dye, pesticide, and petroleum. Cyclohexylamine can be added to boiler water and at concentrations of 5 ppm will prevent corrosion and scaling by maintaining sufficient alkalinity to protect surfaces against carbonic acid. Because CHA forms an azeotrope with water, the chemical enters the steam phase (vapor-phase corrosion inhibitor), thus protecting steam lines and vapor equipment as well as the boiler. Many derivatives of CHA are also used as ferrous corrosion inhibitors (see Appendixes A, B, and D). The rubber industry uses CHA mixed with other chemicals to retard the degradation and discoloration of certain rubber mixtures. Various salts of cyclohexylamine have long been used as vulcanization accelerators (Condensed Chemical Dictionary, 1977; CEH, 1975; Holderried, 1967; Shreve, 1967).

Cyclohexylamine formerly found a good market in the production of sodium and calcium cyclamates, which were used as artificial sweeteners. However, the FDA prohibited the use of cyclamates for this purpose in 1969 (CEH, 1975; Holderried, 1967).

Annual sales figures, as reported by the U.S. International Trade Commission, are as follows: 1971, 4.8 million lb; 1972, 4.2 million lb; 1975, 4.2 million lb. Figures are not available for 1973 and 1974. The producers of CHA are listed in Table 1.

Table 1. Domestic Producers and Suppliers of Cyclohexylamine

| Producer/location | Capacity ($10^6$ lb) |
|---|---|
| Abbott Labs[a,b]<br>Wichita, Kan. | 10 |
| Monsanto Co.[a,b]<br>Sauget, Ill. | 2 |
| Virginia Chemicals, Inc.[a,b]<br>Portsmouth, Va. | 8 |
| Suppliers | |
| BASF Wyandotte, Inc.[b] | Not reported |
| Betz Labs[b] | Not reported |
| Pennwalt Corp.[b] | Not reported |
| Total | 20[c] |

[a] Directory of Chemical Producers (1975).
[b] Chemical Week 1977 Buyers Guide (1976).
[c] Cyclohexylamine and derivatives.

## Health Aspects

### Human

Cyclohexylamine is caustic to skin and mucous membranes, and its systemic effects in man include nausea, vomiting, anxiety, restlessness, and drowsiness (Gleason et al., 1969). Cyclohexylamine may also be a skin sensitizer (Mallette and von Haam, 1952).

In a human volunteer study of CHA, Eichelbaum et al. (1974) found a significant increase in the urinary excretion of catecholamines following the oral administration of 10 mg/kg of CHA. These findings were consistent with others noting the indirectly acting sympathomimetic effects of cyclohexylamine.

The Food and Drug Administration banned the use of cyclamates as artificial sweeteners in 1969 because of their metabolic conversion to cyclohexylamine, which was found to be carcinogenic in rats (Price et al., 1970). There is no evidence that CHA is a human carcinogen.

### Laboratory Animal

Mutagenicity. Cyclohexylamine appears to have potential for chromosome damage. However, the results of studies (both *in vitro* and *in vivo*) conducted over the last several years have been contradictory. Several of the studies are summarized below.

In vitro studies. Cyclohexylamine caused a significant increase in chromosome breaks in cultures of human and Chinese hamster fibroblasts (Bladon and Turner, 1971; Dixon, 1973), in a rat kangaroo cell line (Green et al., 1970), and in human lymphocyte cultures (Stoltz et al., 1970). On the other hand, Brewen et al. (1971) did not observe a significant increase in chromosome aberrations (chromatid breaks) in human lymphocyte cultures, while Schoeller (1971), who noted no significant increase in the frequency of chromosome breaks, observed a considerable increase in chromatid breaks and gaps using a human lymphocyte culture.

In vivo studies. No mutagenic activity was seen in the host-mediated assay by Brewen et al. (1971) or Voogd et al. (1973). The dominant lethal test indicated no mutagenic activity attributable to cyclohexylamine in rats or mice (Bailey et al., 1972; Cattanach and Pollard, 1971; Lorke and Machemer, 1974).

CHA failed to induce sex-linked recessive lethals in Drosophila (Knaap et al., 1973).

Other studies failed to demonstrate an increase in the relative frequency of chromosome aberrations in rat, mouse, or

Chinese hamster spermatogonia (Bailey et al., 1972; Cattanach and Pollard, 1971; Machemer and Lorke, 1976). In support, Dick et al. (1974) found no chromosome-damaging effects caused by CHA in rats or in a group of four human subjects.

Other studies, however, directly contradict these findings with demonstrations of chromosome damage following in vivo administration of CHA. Legator et al. (1969) noted a significant increase in chromosome breaks in the spermatogonia and bone marrow cells of rats; Petersen et al. (1972) found a significant increase in dominant lethal effects in mice; Turner and Hutchinson (1974) indicated an increase in chromosome abnormalities in peripheral lymphocytes of fetal lambs; van Went-de Vries et al. (1975) found chromosome-damaging effects in Chinese hamsters following oral treatment with CHA.

No clear-cut conclusions as to the mutagenic potential of cyclohexylamine can be reached because of the many conflicting studies. Nevertheless, the van Went-de Vries et al. (1975) study appears the strongest because the purity of their CHA samples was checked by mass spectrometry and the compound, which is easily oxidized, was handled at a low pH (2.2-2.4) and in a nitrogen atmosphere. All other studies reporting the pH of the CHA sample used values between 7.0 and 7.3, which are not optimal conditions. It appears likely that much of the lack of agreement among the published results is attributable to the use of impure CHA (van Went-de Vries et al., 1975).

Carcinogenicity. A 10:1 mixture of sodium cyclamate and sodium saccharin (C/S) was added to the diet of rats in concentrations providing a daily intake of 0, 500, 1,120, or 2,500 mg/kg/day. Many of the rats were found to convert cyclamate to cyclohexylamine. In the 79th week, one-half of the animals in each group were given supplemental amounts of cyclohexylamine hydrochloride in the diet at 25, 56, or 125 mg/kg/day. Papillary transitional cell tumors were found in the urinary bladders of 8 of the initial 80 rats receiving 2,500 mg/kg/day of the C/S mixture. In all but one instance, the tumors developed in rats that were found to convert cyclamate to CHA. There were three bladder tumors in rats that received the CHA supplements and five in those that did not (Price et al., 1970).

Cyclohexylamine sulfate was fed in the diet to groups of 50 rats at daily doses of 0, 0.15, 1.5, and 15.0 mg/kg. At the end of the 2 years, CHA-related organ changes were noted only in rats receiving the highest dosage. A single bladder tumor (transitional cell carcinoma, grade 2) was found in one of the eight male survivors in the high-dose group. Spontaneous bladder tumors have never been recorded in control rats at the testing facility (Industrial Bio-Test Laboratories) and are reported to be rare (Price et al., 1970).

This finding of carcinogenic activity attributable to cyclohexylamine has not been supported by the results of subsequent investigators. The results of four studies are summarized in Table 2. These studies are discussed further under "Chronic Toxicity."

Fertility and Teratogenic Effects. Cyclohexylamine has been shown by several investigators to affect male fertility in rats (Khera and Stoltz, 1970; Khera et al., 1971; Green et al., 1972; Oser et al., 1976). These studies demonstrated that males treated with cyclohexylamine (or its sulfate or hydrochloride salt) produced smaller litters than untreated males. CHA was not found to affect the fertility of female rats.

Pregnant female rats were given daily oral doses of CHA (1.8, 3.6, 18.0, or 36.0 mg/kg/day) for a period of 7 days corresponding to the 7th through 13th days of gestation. No significant differences were seen between the treated and control groups in maintenance of pregnancy, fetal development, resorption, or malformation rates (Tanaka et al., 1973). In a similar experiment, CHA was orally administered to pregnant mice at 20, 50, or 100 mg/kg/day for 6 days either from day 0 to day 5 or from day 6 to day 11 of gestation. Cyclohexylamine once again failed to exhibit any teratogenic effects in any of the groups. At 100 mg/kg/day, however, CHA significantly decreased the body weight of living fetuses and was also embryolethal when administered from day 6 to day 11 of gestation (the level of embryotoxicity of CHA was about the same as its subacute toxicity in the adult female) (Takano and Suzuki, 1971).

Chronic Toxicity. Some results of recent carcinogenesis studies on CHA have yielded the following values: 150 mg/kg/day for rats in a two year time period (Oser et al., 1972); 300 in same conditions (Gaunt et al., 1976); and 400 for mice in an 80-week period (Hardy et al., 1976). The conclusion for each study was negative. Growth retardation at the higher levels was the only noted effect of cyclohexylamine on the test animals.

Multigeneration ($F_1$ through $F_4$) rat studies conducted with CHA at dosages of 0, 15, 50, 100, or 150 mg/kg/day over a 2-year period yielded results that were substantially within normal limits. Nonprogressive growth retardation and a slight reduction in litter size and weanling weights were the only changes evident in the highest dosage groups (Bailey et al., 1972; Oser et al., 1976).

Acute and Subacute Toxicity. Watrous and Schulz (1950) exposed rabbits, guinea pigs, and rats to CHA vapors for 7 hr/day, 5 days/week, at an average concentration of 150, 800, or 1,200 ppm. At the highest level, all animals except one rat showed extreme irritation and died after a single exposure. Fractional mortality occurred after repeated exposures at 800 ppm. At 150 ppm, four of five rats and two guinea pigs survived 70 hr of exposure; however, one rabbit died after only 7 hr. The chief effects were irritation of the respiratory tract and eye irritation with the development of corneal opacity. No convulsions were observed.

The IP $LD_{50}$ of CHA in mice was 619 mg/kg, and the lethal dose for rats and dogs was estimated at 350 mg/kg IP and 200 mg/kg IV, respectively. Smaller IV doses in the mouse caused nervous system depression and slight paralysis in the hindlegs (also exhibited by dogs given 5-50 mg/kg of CHA). In all cases, death was attributed to respiratory arrest. Cyclohexylamine caused liberation of histamine in all three animal species as evidenced by severe scratching. In addition, CHA produced a rise in blood pressure and increased cardiac contractile force through release of endogenous catecholamines (Miyata et al., 1969).

A 13-week feeding study with CHA at approximately 30, 100, or 300 mg/kg/day produced growth retardation and reduced testis weight in rats receiving the two highest dosages. The reduced testis weight at the highest level was accompanied by histopathological evidence of reduced spermatogenesis, amounting to complete arrest and loss of the germinal epithelium in 40% of the rats given 300 mg/kg/day. Despite this development, a limited reproduction study showed no statistically significant differences between the offspring of treated and untreated males (Gaunt et al., 1974).

### Environmental Aspects

Little or no information was available on the environmental impact of cyclohexylamine. A study by Jungclaus et al. (1976) identified CHA in the effluent from a tire-manufacturing plant at an approximate concentration of 0.01 mg/l (±30%).

## APPENDIX A. Dicyclohexylamine

### Dicyclohexylamine

### (di-CHA)

Dicyclohexylamine (di-CHA) is a colorless liquid with a faint amine odor. It has a boiling point of 256°C and is sparingly soluble in water. Dicyclohexylamine is strongly basic ($pK_b = 3.3$) (Merck Index, 1968; Condensed Chemical Dictionary, 1977).

The literature outlines several schemes for the manufacture of dicyclohexylamine. The first process involves the hydrogenation of equimolar amounts of cyclohexanone and cyclohexylamine

(Merck Index, 1968). A second process uses the hydrogenation of aniline in the vapor phase in the presence of a nickel catalyst to produce up to 95% di-CHA (Kouris and Northcott, 1967).

Dicyclohexylamine is a strongly basic secondary amine having a reactive amine group which readily yields N-substituted derivatives. It is widely used as a chemical intermediate. Dicyclohexylamine salts of fatty acids and sulfuric acid have soap and detergent properties useful to the printing and textile industries. Metal complexes of di-CHA are used as catalysts in the paint, varnish, and ink industries. Several vapor-phase corrosion inhibitors are solid di-CHA derivatives. These compounds are slightly volatile at normal temperatures and are used to protect packaged or stored ferrous metals from atmospheric corrosion (Holderried, 1967). Dicyclohexylamine is also used for a number of other purposes: plasticizer; insecticidal formulations; antioxidant in lubricating oils, fuels, and rubber; and extractant (Condensed Chemical Dictionary, 1977).

No annual production figures are available for dicyclohexylamine. The domestic producers are: Abbott Laboratories, Wichita, Kans. (Directory of Chemical Producers, 1975; Chemical Week 1977 Buyers Guide, 1976); Virginia Chemicals Inc., Portsmouth, Va. (Directory of Chemical Producers, 1975); BASF Wyandotte, Inc.; and Monsanto Co.

Dicyclohexylamine is somewhat more toxic than cyclohexylamine. Poisoning symptoms and death appear earlier in rabbits injected with 0.5 g/kg di-CHA (as opposed to CHA). Doses of 0.25 g/kg are just sublethal, causing convulsions and reversible paralysis. Dicyclohexylamine is a skin irritant (Carswell and Morrill, 1937).

Pliss (1958) conducted a series of animal experiments with di-CHA. The first involved mice which received daily subcutaneous injections of 0.05 ml of a 2.6% oily solution of di-CHA. The mice often showed transient convulsions following the injection. Of the original 57 mice, 15 were alive after 12 months. At this time, several of the mice began developing local tumors. Postmortem of several of the mice revealed a high incidence of degenerative changes in the liver and kidneys. The results of this study are summarized below.

| Species of animal (no.) | Route of administration | Duration of administration (months) | Total dosage (mg) | No. of tumors | Type of tumor |
|---|---|---|---|---|---|
| Mice (57) | SC injection | 11-12.5 | 60.1-79.3 | 4 | Sarcomas |
| Rats (50) | Feeding | 12 | 8,875 | 2 | One hepatoma and one sarcoma |

The second part of Pliss's experiment involved a rat feeding study. (For 2 months, administration was actually via subcutaneous injection of 30 mg. However, local tissue necrosis forced the change.) The rats were given 0.5 ml of a 5% oily solution of di-CHA in the food six times a week. Of the 50 original rats, 36 survived for over 12 months, 22 for more than 18 months. Most of the animals died of pneumonia. Among the remaining rats, one developed a liver tumor after 21 months and another developed a sarcoma after 22.5 months. See above for a summary of this aspect of the experiment.

Pliss concluded that di-CHA was rather weakly carcinogenic, since relatively few animals developed tumors and the time span for tumor development was rather long.

## APPENDIX B. Dicyclohexylamine Nitrite

### Dicyclohexylamine nitrite
### (di-CHAN)

Dicyclohexylamine nitrite is a solid nitrite salt having some degree of volatility at room temperature and higher. It is used as a vapor-phase corrosion inhibitor whereby it vaporizes either from the solid state or from solution and offers protection against atmospheric rusting. Wrapping paper, plastic wraps, and other materials may be impregnated with di-CHAN to protect metal parts during packaging and storage (Nathan, 1967; Archer and Wishnok, 1976).

No production figures are available for di-CHAN; however, the Directory of Chemical Producers (1975) lists the Olin Corp., East Alton, Ill., as a producer.

Prolonged exposure to dicyclohexylamine nitrite vapor is reported to lead to changes in the CNS, erythrocytes, and methemoglobinemia and to disturb the functional state of the liver and kidneys of human workers. The author recommends a maximum allowable concentration of 0.2 $mg/m^3$ in the workshop (Paustovskaya et al., 1973).

The $LD_{50}$ of di-CHAN by gavage was 80 mg/kg in mice and 325 mg/kg in rats (Paustovskaya, 1974).

Pliss (1958) reported that di-CHAN is a carcinogen in mice and rats. In the mouse study, each animal received a daily SC injection of 0.1 ml of a 1% aqueous solution of di-CHAN. Transient convulsions and excitement sometimes accompanied the injections. Tumors remote from the site of injection were found in 5 of 54 mice. The first rat study involved once-weekly SC injections of 0.5 ml of a 2% aqueous solution. Remote tumors were found in 7 of 50 rats. In the second rat experiment, di-CHAN was fed daily in the diet, six times a week, as 1 ml of a 3% aqueous solution. One rat out of a population of 30 developed a tumor. The results are summarized below.

| Species of animal (no.) | Route of administration | Duration of administration (months) | Total dosage (mg) | No. of tumors |
|---|---|---|---|---|
| Mice (54) | SC injection | 12-13 | 51-59 | 5 |
| Rats (56) | SC injection | 11-13 | 480-1,195 | 7 |
| Rats (30) | Feeding | 12 | 9,180 | 1 |

Pliss concluded that di-CHAN was weakly active, although all tumors developed at different tissue sites remote from the point of injection.

Marhold et al. (1967) contested Pliss's (1958) finding of carcinogenic activity associated with di-CHAN. In a prolonged feeding experiment, 14.2 mg/kg of di-CHAN was added to the diet of rats 7 days a week for their lifetimes. No tumors were found in the population of 20 rats. A second study was conducted using three dogs which were fed 5-10 mg/kg, 5 days a week for life (dogs were 14 months old at initiation of the experiment). No tumors were found in any of the dogs. Despite the small number of animals studied, and notwithstanding Pliss's results, the authors concluded that dicyclohexylamine nitrite was not a carcinogen (or at best a very weak one, or so the article implies) based on the dose given and the length of the study.

## APPENDIX C. N-Nitrosodicyclohexylamine

### N-nitrosodicyclohexylamine

Any situation in which nitrite ions and a secondary amine (such as dicyclohexylamine) are in contact under acidic aqueous conditions has the potential for production of nitrosamines (Mirvish, 1975). Nitrosodicyclohexylamine may be a contaminant of dicyclohexylamine nitrite and also perhaps of dicyclohexylamine, however, nitrosodicyclohexylamine is not carcinogenic (Norred et al., 1975; Nishie et al., 1974). Its lack of carcinogenicity may be traceable to the presence of only one hydrogen on each carbon alpha to the nitrogen (Lijinsky, 1977).

## APPENDIX D. Other Cyclohexylamine Derivatives

Many other salts of cyclohexylamine are used as vapor-phase corrosion inhibitors. There is very limited information available on these compounds in Western literature; however, the Russians have published a number of studies. Refer to Tables D-1 and D-2 for a summary of the acute toxicity associated with several of these salts.

Table D-1. $LD_{50}$ Values for Cyclohexylamine Derivatives

| Substance | Route | Mouse $LD_{50}$ (mg/kg) | Rat $LD_{50}$ (mg/kg) |
|---|---|---|---|
| CHA-benzoate | Gavage | 1,400 | 3,300 |
| CHA-o-nitrobenzoate | Gavage | 2,075 | -- |
| CHA-m-nitrobenzoate | Gavage | 490 | 4,800 |
| CHA-p-nitrobenzoate | Gavage | 1,590 | 1,950 |
| CHA-3,5-dinitrobenzoate | Gavage | 925 | 1,600 |
| CHA-carbonate | Gavage | -- | 820 |
| CHA-chromate | Gavage | 224 | 228 |

Source: Paustovskaya, 1974.

Table D-2. $LD_{50}$ Values for Dicyclohexylamine Derivatives

| Substance | Route | Mouse $LD_{50}$ (mg/kg) | Rat $LD_{50}$ (mg/kg) |
|---|---|---|---|
| di-CHA-benzoate | Gavage | 290 | 700 |
| di-CHA-o-nitrobenzoate | Gavage | 300 | 925 |
| di-CHA-m-nitrobenzoate | Gavage | 364 | 1,060 |
| di-CHA-p-nitrobenzoate | Gavage | 318 | 1,620 |
| di-CHA-carbonate | Oral | -- | 1,075 |

Source: Paustovskaya, 1974; Garshenin et al., 1973.

The chromates, benzoates, and nitrobenzoates were also found toxic following dermal application. One study indicated that the daily application of 625 mg/kg of CHA-chromate to the shaved skin of rabbits and rats caused the death of five of seven animals within 3-10 days, and the daily application of 1,500 mg/kg CHA-chromate caused the death of all experimental animals within 4 days. Necropsy revealed an enlarged bladder, blood in the urine, and dystrophy of nerve cells, liver, and kidneys (Paustovskaya and Rappoport, 1966).

# REFERENCES

Archer, M. C., and J. S. Wishnok. The nitrous acid test for amines--A potentially hazardous reaction. J. Chem. Educ. 53:559, 1976.

Bailey, D. E. et al. Chronic toxicity, teratology, and mutagenicity studies with cyclohexylamine in rats. Toxicol. Appl. Pharmacol. 22:330, 1972.

Bladon, M. T., and J. H. Turner. Independent and joint effects of caffeine and cyclohexylamine upon (KDCS) WI-38. Mamm. Chrom. Newsl. 12:5, 1971.

Brewen, J. G. et al. Cytogenetic effects of cyclohexylamine and N-hydroxycyclohexylamine on human leukocytes and Chinese hamster bone marrow. Nature New Biol. 230:15, 1971.

Carswell, T. S., and H. L. Morrill. Cyclohexylamine and dicyclohexylamine. Ind. Eng. Chem. 29:1247, 1937.

Cattanach, B. M., and C. E. Pollard. Mutagenicity tests with cyclohexylamine in the mouse. Mutat. Res. 12:472, 1971.

Chemical Economics Handbook (CEH). Menlo Park, Calif., Stanford Research Institute. 1975.

Chemical Week 1977 Buyers Guide, Part 2. New York, McGraw-Hill. 1976.

Condensed Chemical Dictionary, 9th ed. New York, Van Nostrand Reinhold Co. 1977.

Dick, C. E. et al. Cyclamate and cyclohexylamine: Lack of effect on the chromosomes of man and rats *in vivo*. Mutat. Res. 26:199, 1974.

Directory of Chemical Producers. Menlo Park, Calif., Stanford Research Institute. 1975.

Dixon, C. H. *In vitro* effects of sodium and calcium cyclamates, cyclohexylamine and sucrose on growth rate and chromosomes of Chinese hamster fibroblasts. Diss. Abstr. 59-33 B, 1973.

Eichelbaum, M. et al. Pharmacokinetics, cardiovascular and metabolic actions of cyclohexylamine in man. Arch. Toxikol. 31:243, 1974.

Garshenin, V. F. et al. Sanitary-toxicological characteristics of inhibitors of atmospheric corrosion. Gig. Sanit. Okhr. Vodoemov, p. 81, 1973. (Abstract)

Gaunt, I. F. et al. Short-term toxicity of cyclohexylamine hydrochloride in the rat. Food Cosmet. Toxicol. 12(5-6):609, 1974.

Gaunt, I. F. et al. Long-term toxicity of cyclohexylamine hydrochloride in the rat. Food Cosmet. Toxicol. 14:255, 1976.

Gleason, M. et al. Clinical Toxicology of Commerical Products, 3rd ed. Baltimore, The Williams and Wilkins Co. 1969.

Green, S. et al. In vitro cytogenetic investigation of calcium cyclamate, cyclohexylamine and triflupromazine. Food Cosmet. Toxicol. 8:617, 1970.

Green, S. et al. Effects of cyclohexylamine on the fertility of male rats. Food Cosmet. Toxicol. 10:29, 1972.

Hardy, J. et al. Long-term toxicity of cyclohexylamine hydrochloride in mice. Food Cosmet. Toxicol. 14:269, 1976.

Holderried, J. A. Amines. In Kirk-Othmer Encyclopedia of Chemical Technology, vol. 2. New York, Interscience Publishers. 1967. p. 116.

Jungclaus, G. A. et al. Identification of trace organic compounds in the manufacturing of plant waste water. Anal. Chem. 48(13):1894, 1976.

Khera, K. S., and D. R. Stoltz. Effects of cyclohexylamine on rat fertility. Experimentia 26:761, 1970.

Khera, K. S. et al. Reproduction study in rats orally treated with cyclohexylamine sulfate. Toxicol. Appl. Pharmacol. 18:263, 1971.

Knaap, A. G. A. C. et al. Lack of mutagenicity of the cyclamate metabolites in Drosophila. Mutat. Res. 21:341, 1973.

Kouris, C. S., and J. Northcott. Aniline. In Kirk-Othmer Encyclopedia of Chemical Technology, vol. 2. New York, Interscience Publishers. 1967. p. 411.

Legator, M. S. et al. Cytogenetic studies in rats of cyclohexylamine, a metabolite of cyclamate. Science 165:1139, 1969.

Lijinsky, William. How nitrosamines cause cancer. New Sci. January 1977, p. 216.

Lorke, D., and L. Machemer. Investigation of cyclohexylamine sulfate for dominant lethal effects in the mouse. Toxicology 2:231, 1974.

Machemer, L., and D. Lorke. Evaluation of the mutagenic potential of cyclohexylamine on spermatogonia of the Chinese hamster. Mutat. Res. 40(3):243, 1976.

Mallette, F. S., and E. von Haam. Studies on the toxicity and skin effects of compounds used in the rubber and plastics industries. I. Accelerators, activators, and antioxidants. Arch. Ind. Hyg. Occup. Med. 5:311, 1952.

Marhold, J. et al. On the carcinogenicity of dicyclohexylamine. Neoplasma 14(2):177, 1967.

Merck Index. Rahway, N.J., Merck and Co. 1968.

Mirvish, S. S. Toxicol. Appl. Pharmacol. 31:325, 1975.

Miyata, T. et al. Pharmacological characteristics of cyclohexylamine, one of the metabolites of cyclamate. Life Sci. 8(1):843, 1969.

Nathan, C. C. Corrosion inhibitors. In Kirk-Othmer Encyclopedia of Chemical Technology, vol. 6. New York, Interscience Publishers. 1967. p. 317.

Nishie, K. et al. Effect of short-term administration of n-nitroso compounds on liver histology and on pentobarbital-induced sleeping time in mice. Res. Commun. Chem. Pathol. Pharmacol. 8(2):301, 1974. (Abstract)

Norred, W. P. et al. Effect of short-term administration of nitrosamines on rat hepatic microsomal enzymes. Biochem. Pharmacol. 24(13-14):1313, 1975.

Oser, L. et al. Long-term and multigeneration toxicity studies with cyclohexylamine hydrochloride. Toxicology 6:47, 1976.

Patty, F. A. (ed.). Industrial Hygiene and Toxicology, vol. 2. New York, Interscience Publishers. 1963.

Paustovskaya, V. V. The toxicity of inhibitors of atmospheric corrosion of metals. Prot. Met. 10(3):310, 1974. (English translation, March 1975)

Paustovskaya, V. V., and M. B. Rappoport. Toxicity of cyclohexylamine chromate entering through the skin. Vrach. Delo 1:149, 1966. (Abstract)

Paustovskaya, V. V. et al. Hygienic characteristics of the working conditions when protecting metalware with rust inhibitor dicyclohexylamine nitrite. Gig. Tr. Prof. Zabol. 17(1):35, 1973. (Abstract)

Petersen, K. W. et al. Dominant-lethal effects of cyclohexylamine in C57 Bl/Fe mice. Mutat. Res. 14:126, 1972.

Pliss, G. B. The carcinogenic activity of dicyclohexylamine and its nitrite salt. Probl. Oncol. 4(6):22, 1958.

Price, J. M. et al. Bladder tumors in rats fed cyclohexylamine or high doses of a mixture of cyclamate and saccharin. Science 167:1131, 1970.

Schoeller, L. Chromosomal effects of cyclohexylamine. Wiss. Veroeff. Dtsch. Ges. Ernaehr. 20:125, 1971. (Abstract)

Shreve, R. N. Amination by reduction. *In* Kirk-Othmer Encyclopedia of Chemical Technology, vol. 2. New York, Interscience Publishers. 1967. p. 76.

Smyth, H. F. et al. Range-finding toxicity data: List VII. Am. Ind. Hyg. Assoc. J. 30:470, 1969.

Stoltz, D. R. et al. Cytogenetic studies with cyclamate and related compounds. Science 167:1501, 1970.

Takano, K., and M. Suzuki. Cyclohexylamine, a chromosome-aberration inducing substance: No teratogenicity in mice. Congenital Anomalies 11(2):51, 1971.

Tanaka, S. et al. Studies on the teratogenicity of food additives (2). J. Food Hyg. Soc. 14(6):542, 1973.

Turner, J. H., and D. L. Hutchinson. Cyclohexylamine mutagenicity: An *in vivo* evaluation utilizing fetal lambs. Mutat. Res. 26:207, 1974.

U.S. International Trade Commission. Synthetic Organic Chemicals. 1971, 1972, 1975.

van Went-de Vries, G. et al. *In vivo* chromosome-damaging effect of cyclohexylamine in the Chinese hamster. Food. Cosmet. Toxicol. 13:415, 1975.

Voogd, C. E. et al. Investigation of mutagenic activity of sodium cyclamate, sodium saccharinate and cyclohexylamine. Natl. Inst. Public Health Rep. 15/73 Chemo.

Watrous, R. M., and H. N. Schulz. Ind. Med. Surg. 19:317, 1950. (As cited in Patty, 1963)

# CHEMICAL HAZARD INFORMATION PROFILE

## 1,6-Diaminohexane

Date of report: June 6, 1978

This chemical was chosen for study because of its possible presence in consumer products and its potential for nitrosamine formation.

The following recommendations are made regarding further OTE evaluation of the possible health or environmental hazards of 1,6-diaminohexane:

(1) Require TSCA Section 8(a) submission--Better information is needed on uses so that EPA can estimate the extent of nonoccupational exposure to this chemical.

(2) Consider need for testing--Diaminohexane is a high-volume chemical which has demonstrated toxic effects at low doses.

(3) Transmit to NIOSH on an FYI basis--NIOSH has scheduled a criteria document for aliphatic di- and polyamines.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

## Chemical Identity

1,6-Diaminohexane (hexamethylenediamine), $C_6H_{16}N_2$, is a colorless, combustible solid which melts at 39-42°C. It is somewhat soluble in water, ethanol, and ether (Hawley, 1971).

## Production and Use

Diaminohexane can be manufactured in two ways (Hawley, 1971):

(1) Reaction of adipic acid and ammonia (catalytic vapor phase) to yield adiponitrile, followed by liquid-phase catalytic hydrogenation.

(2) Chlorination of butadiene followed by reaction with sodium cyanide (cuprous chloride catalyst) to 1,4-dicyanobutylene, and hydrogenation.

The production volume of diaminohexane was 750 million lb in 1975 (U.S. International Trade Commission, 1977). The 1975 Directory of Chemical Producers lists the following manufacturers of diaminohexane (SRI, 1976): Celanese Corp., Celanese Chemical Co. Division, Bay City, Tex.; E. I. du Pont de Nemours & Co., Inc., Polymer Intermediates Department, Orange, Tex., and Victoria, Tex.; El Paso Natural Gas Co., El Paso Products Co., subsidiary, Odessa, Tex.; Monsanto Co., Monsanto Textiles Co., Pensacola, Fla.; and R.S.A. Corp., Ardsley, N.Y.

Celanese Chemical Co. states that diaminohexane is used as a raw material for nylon fiber and plastics; in the manufacture of oil-modified and moisture-area types of urethane coatings; in the manufacture of polyamides for printing inks, dimer acids, and textiles; and as an oil and lubricant additive (probably as a corrosion inhibitor) (McCurdy, 1977). Diaminohexane is also used in paints and as a curing agent for epoxy resins (Tkachenko, 1976).

## Health Aspects

Continuous 90-day inhalation of 1 $mg/m^3$ of diaminohexane by albino rats caused an increase in the number of reticulocytes (only at the beginning of the exposure) and an increase in the Vi antibody concentration. The animals also exhibited a decrease in the number of eosinophils, suppressed leukocytic activity, retarded growth, and a disturbance of the chronaxy correlation of the muscle antagonists. Diaminohexane at a concentration of 0.04 $mg/m^3$ caused similar but less pronounced changes. Diaminohexane at 0.001 $mg/m^3$ had no effect (Kulakov, 1965).

Exposure of rats to an atmosphere containing 1.25 $mg/m^3$ diaminohexane for 4 hr/day for 8 days decreased the threshold of neuromuscular excitability, increased blood leucocyte and liver glycogen levels, caused disorders of renal excretory capacity, and altered the phagocytic activity of neutrophils (Tkachenko, 1976).

Diaminohexane inhibited DNA and RNA formation in vitro in studies using rat embryo and human amnion cell cultures (Trakhtenberg et al., 1976).

Intraperitoneal injection of diaminohexane into rats inhibited ovarian ornithine decarboxylase activity which had been stimulated by human chorionic gonadotropin (Guha and Janne, 1977). Diaminohexane injected into mice bearing ascites-carcinoma cells powerfully decreased ornithine decarboxylase activity in the carcinoma cells (Kallio et al., 1977).

An in vitro study showed that diaminohexane inhibited collagen-induced human platelet aggregation (Jobin and Tremblay, 1969).

Occupational exposure to epoxy resins and their hardeners (including diaminohexane) was studied in 488 workers. Prolonged contact caused skin damage, allergic rhinitis, bronchial asthma, impairment of bronchial permeability, toxicoallergic hepatitis, gastritis, colitis, hypergammaglobulinemia, increased transaminase activity, and eosinophilia of the peripheral blood (Gul'ko, 1971).

## Environmental Aspects

The estimated release rate of diaminohexane to the environment is 12.8 million lb/year. Diaminohexane is reactive toward oxidizing agents (Dorigan et al., 1976).

## REFERENCES

Dorigan, J., B. Fuller, and R. Duffy. Scoring of Organic Air Pollutants. Chemistry, Production, and Toxicity of Selected Synthetic Organic Chemicals. 1976.*

Guha, S. K., and J. Janne. Inhibition of ornithine decarboxylase in vivo in rat ovary. Biochem. Biophys. Res. Commun. 75(1): 136-142, 1977. (As stated in CBAC abstract)

Gul'ko, S. N. Damage to respiratory organs under the occupational effects of epoxide resins. Klin. Med. 49(12):107-109, 1971. (As stated in HEEP abstract)

Hawley, G. G. (ed.). The Condensed Chemical Dictionary, 8th ed. New York, Van Nostrand Reinhold Co. 1971.

Jobin, F., and F. Tremblay. Platelet reactions and immune processes. II. Inhibition of platelet aggregation by complement inhibitors. Thromb. Diath. Haemorrh. 22(3):466-481, 1969. (As stated in CBAC abstract)

Kallio, A., H. Poso, S. K. Guha, and J. Janne. Polyamines and their biosynthetic enzymes in Ehrlich ascites-carcinoma cells. Modification of tumour polyamine pattern by diamines. Biochem. J. 166(1):89-94, 1977. (As stated in author abstract)

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*This document was prepared for the U.S. Environmental Protection Agency by the MITRE Corp. It is a secondary source and does not cite its primary references. Thus, verification of some information is not possible. The environmental release data were taken from the NSF/Rann Research Program on Hazard Priority Ranking of Manufactured Chemicals.

Kulakov, A. E. The effect of small concentrations of hexamethylenediamine on experimental animals under conditions of chronic inhalation poisoning. Gig. Sanit. 30(5):15-20, 1965. (English translation)

McCurdy, P. P. (ed.). Chemical Week 1978 Buyers Guide. New York, McGraw-Hill, Inc. 1977.

SRI International. Directory of Chemical Producers. Menlo Park, Calif., Stanford Research Institute. 1976.

Tkachenko, A. E. Experimental data on the nature of the primary response of an animal under the effect of hexamethylenediamine. Gig. Tr. Prof. Zabol. 12:51-52, 1976. (As stated in CBAC abstract)

Trakhtenberg, I. M., I. S. Brit, and Y. I. Morgunova. Use of spectral microanalysis of cell cultures for evaluating the comparative toxicity of new chemical substances. Gig. Sanit. 10:54-56, 1976. (As stated in CBAC abstract)

U.S. International Trade Commission. Synthetic Organic Chemicals. U.S. Production and Sales, 1975. U.S. ITC Publ. No. 804. 1977.

# CHEMICAL HAZARD INFORMATION PROFILE

## 1,2-Dichloroethane

Date of report: September 1, 1977

This chemical was chosen for study because of its high production volume.

It is recommended that OTS continue its ongoing hazard assessment of 1,2-dichloroethane and then proceed to a Phase I report. The reasons for concern about 1,2-dichloroethane are its potential carcinogenicity and its high rate of release into the environment. A requirement for TSCA Section 8(d) submissions is also recommended in order to improve the base of information for Phase I assessment.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

### Chemical Identity

1,2-Dichloroethane (DCE) is a colorless oily liquid with a chloroform-like odor. It is stable to water, acids, and bases, and also resists oxidation. Ethylene dichloride is miscible with most common solvents but is only slightly soluble in water. It has a boiling point of 83.5°C. In 1975, DCE was the 16th highest volume chemical produced in the United States (CCD, 1977).

### Production and Use

1,2-Dichloroethane is produced by the vapor- or liquid-phase reaction of chlorine with ethylene in the presence of a catalyst. When chlorine is combined with ethylene, both substitution and addition reactions occur; ethylene dichloride is the major product only under certain conditions. In a representative industrial scheme, chlorine (combined with ethylene dibromide and heated to 50°C) reacts with a stream of ethylene gas and is passed to a condenser. The ethylene dibromide liquefies and is recycled. DCE is subsequently condensed and purified by fractional distillation. The yield is approximately 96-98%. Metallic chlorides (e.g., ferric, aluminum, copper, or antimony) are commonly used as the catalyst. Most commercial producers currently use a ferric chloride catalyst in a liquid-phase process.

When considerable excess hydrogen chloride is available, the oxychlorination of ethylene is the preferred method of DCE synthesis. This process reacts ethylene, hydrogen chloride, and air in a fluidized or fixed-bed catalytic process. The catalyst is copper chloride (SRI, 1975; Hardie, 1967; Lowenheim and Moran, 1975).

Table 1 lists the major producers of 1,2-dichloroethane in the United States. The available supply of DCE for the merchant market is less than the production capacities contained in Table 1 because only the 1,2-dichloroethane produced by the direct chlorination of ethylene can be isolated and sold. 1,2-Dichloroethane manufactured via the oxychlorination of ethylene is used captively as an intermediate in vinyl chloride production and cannot be separated from that production (SRI, 1975). Table 2 offers a compilation of production and sales figures for DCE over the last several years.

Table 1. DCE Producers, Plant Locations, and Capacities

| Producers and plant locations | Capacity as of 12/74 ($10^6$ lb) |
|---|---|
| Allied Chemical Corp. | |
| Baton Rouge, La. | 650 |
| American Chemical Corp. | |
| Long Beach, Calif. | 300 |
| Conoco Chemicals | |
| Lake Charles, La. | 1,000 |
| Diamond Shamrock Chem. Co. | |
| Deer Park, Tex. | 260 |
| Dow Chemical U.S.A. | |
| Freeport, Tex./Oyster Creek, Tex. | 2,400 |
| Plaquemine, La. | 1,160 |
| Ethyl Corp. | |
| Houston, Tex. | 260 |
| Baton Rouge, La. | 550 |
| B.F. Goodrich Chem. Co. | |
| Calvert City, Ky. | 1,000 |
| PPG Industries | |
| Lake Charles, La. | 1,000 |
| Guayanilla, P.R. | 835 |
| Shell Chem. Co. | |
| Deer Park, Tex. | 1,200 |
| Norco, La. | 1,165 |
| Union Carbide Corp. | |
| Taft, La. | 150 |
| Texas City, Tex. | 150 |
| Vulcan Materials Co. | |
| Geismar, La. | 240 |
| Total | 12,320 |

Source: SRI, 1975.

Table 2. Production[a] and Sales of DCE ($10^6$ lb)

| Year | Production | Sales |
|---|---|---|
| 1960[b] | 1,267 | 438 |
| 1965[b] | 2,850 | 309 |
| 1970[c] | 7,460 | 1,314 |
| 1973[c] | 9,293 | 1,351 |
| 1974[c] | 9,165 | 1,314 |
| 1975[c,d] | 7,977 | 762 |

[a] Production totals may be understated because some EDC is produced but not separated or accurately measured and, therefore, not accurately reported by some producers.

[b] SRI, 1975

[c] U.S. International Trade Commission, 1970, 1973, 1974, 1975.

[d] Reasons for the production decline are not clear; however, the drop-off may only reflect short-term recessionary influences.

The great majority of all 1,2-dichloroethane produced in the United States is used as the starting material in the manufacture of vinyl chloride monomer (VCM). Formerly, DCE, either by itself or in combination with other solvents, was of considerable importance as a commercial solvent and extractant. At this time, however, 1,2-dichloroethane has been replaced in these applications by methyl chloroform, trichloroethylene, and perchloroethylene, all of which are made from ethylene dichloride. Other important commercial products derived from ethylene dichloride include vinylidene chloride and ethyleneamines. Formulations of tetraethyl lead, the gasoline antiknock additive, incorporate DCE as a lead scavenger. This application of DCE is expected to continue to decline because of the phasing out of leaded gasolines. Miscellaneous uses of 1,2-dichloroethane include solvent applications (e.g., textile cleaning, metal degreasing, and in some formulations of acrylic-type adhesives), production intermediate for polysulfide elastomers, constituent of nitrile and polysulfide rubber cements, component of upholstery and carpet fumigants, and in the manufacture of grain fumigants (SRI, 1975; Gleason et al., 1969). Additional uses reported in the Condensed Chemical Dictionary (1977) include: paint, varnish, and finish removers; soaps and scouring compounds; wetting and penetrating agents; and ore flotation. See Table 3 for a listing of the major uses of ethylene dichloride; Table 4 presents a breakdown of the consumption patterns for 1974 and 1976.

Table 3. DCE Consumption Pattern (%)

| | 1974 | 1976 |
|---|---|---|
| Vinyl chloride | 81 | 86 |
| Methyl chloroform | 3 | 3 |
| Trichloroethylene | 3 | 2 |
| Perchloroethylene | 3 | 2 |
| Vinylidene chloride | 2 | - |
| Ethyleneamines | 3 | 3 |
| Lead scavenger | 2 | 2 |
| Miscellaneous | neg. | - |
| Exports | 3 | - |
| | 100 | 100 |

Adapted from: SRI, 1975; EPA, 1977a.

Domestic consumption of DCE is projected to increase by an estimated 4% annually through 1979. Currently, over 90% of the vinyl chloride produced in the United States is based on DCE; the remainder is manufactured by the addition of hydrogen chloride to acetylene. The latter process was responsible for 48% of U.S. vinyl chloride production in 1963 and could be used to replace the currently favored DCE route (U.S. EPA, 1977a).

## Health Aspects

### Human

The primary effects of DCE exposure are CNS depression and gastrointestinal upset. These symptoms are characteristic of acute, subacute, and chronic exposure to 1,2-dichloroethane. Liver, kidney, and adrenal injuries occur in a dose-related fashion. The symptom of nausea and vomiting is quite striking and is similar to that seen from carbon tetrachloride (Irish, 1963).

The NIOSH Criteria Document on 1,2-dichloroethane (1976) is replete with documented cases of fatal and nonfatal human exposure to ethylene dichloride. Most of the injurious exposures were acute episodes and occurred through either accidental or industrial exposure. Ingestion of 20 to 50 ml (30-70 g) of DCE is often fatal within a few days at most (Gleason et al., 1969). Blood disorders appear characteristic of DCE ingestion, with clotting difficulties being the most common. Death is often attributed to circulatory and respiratory failure, with varying degrees of liver and kidney damage (NIOSH, 1976).

The effects of acute exposure to DCE by skin absorption and inhalation are similar to those seen following ingestion, although blood disorders are less prominent. Headache, weakness, eye irritation, cyanosis, nausea, and vomiting appear first, followed by loss of consciousness and respiratory and circulatory failure. Postmortem findings often include damage to the liver, kidneys, and lungs (NIOSH, 1976).

Although fatal cases have been reported following chronic exposure to DCE, fatalities are more commonly associated with acute episodes. Nonetheless, progressive chronic effects can result if DCE exposure is not adequately limited. Rosenbaum (1947) reported that symptoms of acute exposure can rapidly develop following several exposures to 75-125 ppm of DCE. A number of Rosenbaum's cases resulted in death when the worker experienced acute poisoning symptoms two or more times over a 2- to 3-week period. Urosova (1953) reported that 1,2-dichloroethane appeared in the milk of nursing mothers who were occupationally exposed to DCE by inhalation and skin adsorption. In a related experiment, the author measured the amount of DCE in breath and milk samples from a woman exposed to approximately 15.5 ppm of 1,2-dichloroethane for an unspecified length of time. Eighteen hours following the exposure, 0.20-0.63 mg/100 ml 1,2-dichloroethane was found in her milk and 0.01-0.02 mg/l (2-4 ppm) was found in her breath.

### Animal

Animal studies with DCE have demonstrated effects similar to those reported in humans, including narcosis, pulmonary congestion and edema, blood clotting disorders, and liver, adrenal, and kidney damage (NIOSH, 1976; Irish, 1963). Heppel et al. (1944) demonstrated corneal clouding in dogs following DCE exposure; however, this has not been observed in humans.

EPA was officially notified by NCI on November 14, 1977, of the preliminary results of a 90-day rat and mouse feeding study. The preliminary findings were as follows:

Rat--Male: Squamous cell cancer of the forestomach; hemangiosarcomas at all sites, e.g., liver, spleen. Female: Mammary adenocarcinoma.

Mouse--Male: Hepatocellular carcinoma? Lung adenoma? Hepatocellular carcinoma? Lung adenoma? Female: Mammary adenocarcinoma; lung adenoma? Endometrial polyps?

1,2-Dichloroethane was also studied as part of NCI's biossay program. DCE was administered by gastric intubation to mice and rats of both sexes five times per week over a period of 78 weeks. The following dose levels were used:

| Species | Sex | Low dose | High dose |
|---|---|---|---|
| Rat | M&F | 50 mg/kg | 100 mg/kg |
| Mouse | M | 100 | 200 |
|  | F | 150 | 300 |

The study has not been finalized; however, the preliminary results described below appear to indicate that DCE is carcinogenic in both species.

Male rats developed statistically significant numbers of squamous cell carcinomas of the forestomach (a rare growth in the rat species tested) as well as statistically significant numbers of hemangiosarcomas of the circulatory system. Female mice and rats, on the other hand, developed statistically significant numbers of mammary gland adenocarcinomas. The tentative conclusion of the bioassay report is that DCE is a carcinogen in male and female rats and female mice (Dr. Sidney Siegel of NCI, meeting presentation, December 15, 1977).

The tumors observed in the DCE experiment are similar to those seen by Olson et al. (1973) in their gastric intubation study of ethylene dibromide (EDB), the brominated analog of DCE. However, the growths observed in the DCE study were not as dramatic as those associated with EDB in terms of both the numbers of tumors observed and the rapidity of their development (Dr. Ciprieno Cueto of NCI, personal communication, November 3, 1977; Dr. Sidney Siegel of NCI, meeting presentation, December 15, 1977).

1,2-Dichloroethane has been shown to be weakly mutagenic in bacteria without metabolic activation (Voogd et al., 1972; Voogd, 1973; Brem et al., 1974; Rosenkranz et al., 1974). Attempts to increase the bacterial mutagenic activity of DCE using a rat liver homogenate for activation (Ames test) were unsuccessful. The authors ascribed the difficulty to metabolic inefficiencies in the *in vitro* system (McCann et al., 1975). The major metabolic products of DCE in mammalian systems have been tentatively identified as chloroacetic acid, chloroethanol, and chloroacetaldehyde (Yllner, 1971; Heppel and Porterfield, 1948). In the Ames test, chloroacetic acid was negative while chloroethanol responded weakly, in similar fashion to DCE. Chloroacetaldehyde, however, was hundreds of times more effective than DCE or chloroethanol (on a molar basis) in reversion of *Salmonella* bacterial strains (McCann et al., 1975).

Chloroacetaldehyde and chloroethylene oxide have been implicated as likely *in vitro* metabolites of vinyl chloride (Gothe et al., 1974). Chloroethylene oxide is known to rearrange spontaneously to chloroacetaldehyde (Zief and Schramm, 1964). Furthermore, both compounds have been found mutagenic in the Ames test (McCann et al., 1975; Malaveille et al., 1975), suggesting that one or both of these metabolites may be the true active carcinogenic form of vinyl chloride (McCann et al., 1975). If the preceding is verified and chloroacetaldehyde is found to be the active metabolite of both DCE and vinyl chloride, the implications for DCE would obviously be of great significance. McCann et al. (1975) reported that chloroacetaldehyde, on the basis of its potent mutagenic activity, is likely to be a carcinogen and should be evaluated for its carcinogenic potential. Lawrence et al. (1972), in an extensive study of chloroacetaldehyde, observed lung changes in exposed rats that are suggestive of a premalignant condition.

In mutagenic studies, 1,2-dichloroethane displays greater killing and mutagenic effectiveness than monofunctional agents (such as methyl methanesulfonate). This phenomenon (shared by neutrons and bifunctional alkylating agents, among others) has been described as "genetic death" and is characterized by the ability to cause considerable damage to DNA and equal damage to proteins (as measured by enzyme inactivation). As an example, consider ethylene oxide and diepoxybutane: while both exhibit the same approximate immediate toxicity, the bifunctional agent provokes a delayed killing response that renders diepoxybutane two orders of magnitude more toxic at the stage of maturity of barley plants (in this instance). This difference can be explained in terms of the severe consequences of the cross-linking of DNA, especially with respect to the inability of exposed cells to duplicate DNA and perform mitosis. Furthermore, cross-linking may follow primary alkylation at a site which is not, per se, considered to be involved in mutagenesis, and thus the effect of the bifunctional agent is considerably enhanced over that seen for monofunctional chemicals (Ehrenberg et al., 1974).

## Environmental Aspects

The annual release of DCE to the environment has been estimated in two EPA-sponsored reports. One investigation (U.S. EPA, 1976a) estimates that 560 million lb of DCE was released domestically in 1973. The second report (U.S. EPA, 1975a) claims that the actual release rate of DCE is somewhat lower, with 163 million lb released in 1974. This latter figure was generated in a more careful fashion since losses from several specific categories were considered, whereas the first report used only percentages of production and consumption. In the second EPA report, emissions of DCE during the manufacture of end products, principally vinyl chloride, were identified as the major source of environmental losses. Production of DCE was cited as the next largest emissions category. Of the two processes used to manufacture DCE, the oxychlorination method was felt to emit five times as much DCE as the direct chlorination scheme for the same quantity of product. The third major source of DCE emissions was its use as a solvent (100% losses assumed). Storage and distribution of DCE were identified as the last major loss category. Refer to Table 4 for further information.

Table 4. 1,2-Dichloroethane Emissions Estimate
(based on 1974 domestic DCE production of 9,300 million lb)

| Source | Source strength ($10^6$ lb) | % Loss | DCE emissions ($10^6$ lb) |
|---|---|---|---|
| End product mfg. | 8,500 | 1.0 | 85.0 |
| DCE production | | | |
| Oxychlorination | 3,906 | 1.2 | 48.3 |
| Direct chlorination | 5,394 | 0.2 | 9.7 |
| Solvent uses | 14 | 100 | 14 |
| Storage/distribution | 9,300 | 0.06 | 6 |
| Total | | | 163 |

Source: EPA, 1975a.

Figure 1 presents a schematic of the losses and waste products associated with vinyl chloride production. Waste streams 4 and 5 in the figure represent the most hazardous process wastes associated with vinyl chloride production. These "heavy ends" (often called DCE tars) are most commonly disposed of via uncontrolled incineration in the United States. This is not considered an environmentally adequate method, as controlled incineration practices will reduce air pollution while having no impact on water and noise pollution (U.S. EPA, 1976b).

In some European countries, DCE tars are dumped in ocean waters (e.g., the North Sea) where the tars may have adverse effects on the marine environment (Jensen et al., 1975). This method of disposal is apparently not used in the United States, although this could not be confirmed.

1,2-Dichloroethane, being a vicinal or neighboring dihalide, is virtually unreactive in water. The half-life of DCE in water (via chemical degradation only) is estimated to be on the order of thousands of years (U.S. EPA, 1977b).

DCE has been found in 11 raw water locations at levels from less than 0.2 to 3.1 μg/l and in 26 finished water locations (32.0 of total) at levels ranging from 0.2-6.0 μg/l (U.S. EPA,

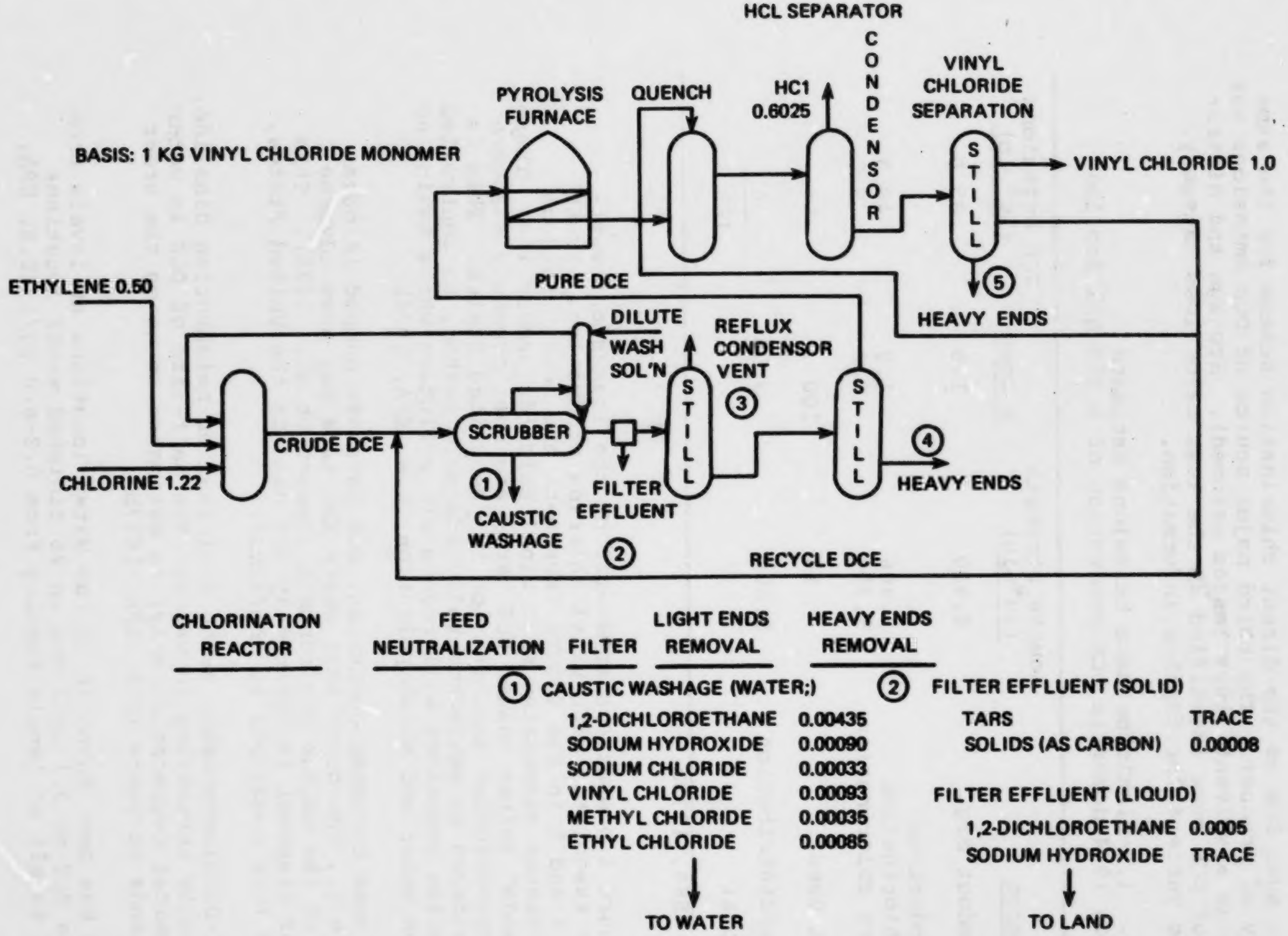
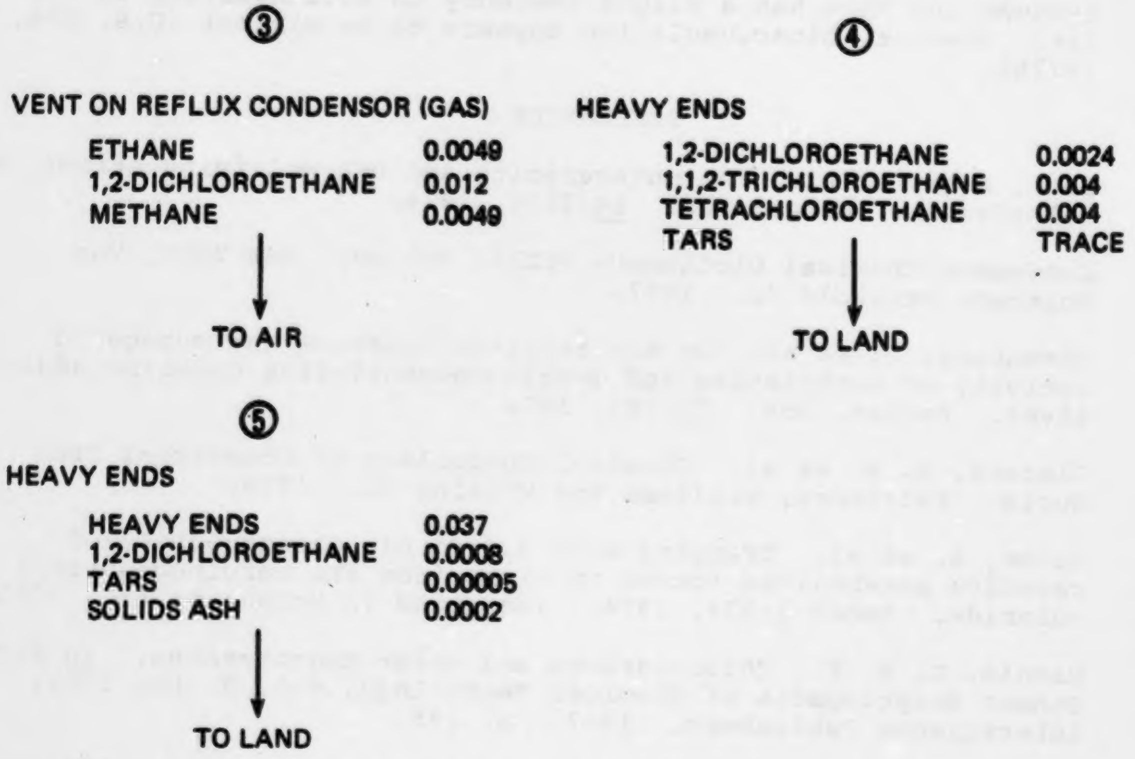

BASIS: 1 KG VINYL CHLORIDE MONOMER
ETHYLENE 0.50
CHLORINE 1.22
CRUDE DCE
PYROLYSIS FURNACE
QUENCH
HCL SEPARATOR
HC1 0.6025
CONDENSOR
VINYL CHLORIDE SEPARATION
STILL
VINYL CHLORIDE 1.0
⑤
HEAVY ENDS
PURE DCE
DILUTE WASH SOL'N
SCRUBBER
①
CAUSTIC WASHAGE
FILTER EFFLUENT
②
REFLUX CONDENSOR VENT
③
STILL
④
HEAVY ENDS
RECYCLE DCE
CHLORINATION REACTOR
FEED NEUTRALIZATION
FILTER
LIGHT ENDS REMOVAL
HEAVY ENDS REMOVAL
① CAUSTIC WASHAGE (WATER;)
1,2-DICHLOROETHANE 0.00435
SODIUM HYDROXIDE 0.00090
SODIUM CHLORIDE 0.00033
VINYL CHLORIDE 0.00093
METHYL CHLORIDE 0.00035
ETHYL CHLORIDE 0.00085
TO WATER
② FILTER EFFLUENT (SOLID)
TARS TRACE
SOLIDS (AS CARBON) 0.00008
FILTER EFFLUENT (LIQUID)
1,2-DICHLOROETHANE 0.0005
SODIUM HYDROXIDE TRACE
TO LAND

Figure 1. Vinyl chloride monomer manufacture.

Source: EPA, 1975b.



③

VENT ON REFLUX CONDENSOR (GAS)

| | |
|---|---|
| ETHANE | 0.0049 |
| 1,2-DICHLOROETHANE | 0.012 |
| METHANE | 0.0049 |

TO AIR

④

HEAVY ENDS

| | |
|---|---|
| 1,2-DICHLOROETHANE | 0.0024 |
| 1,1,2-TRICHLOROETHANE | 0.004 |
| TETRACHLOROETHANE | 0.004 |
| TARS | TRACE |

TO LAND

⑤

HEAVY ENDS

| | |
|---|---|
| HEAVY ENDS | 0.037 |
| 1,2-DICHLOROETHANE | 0.0008 |
| TARS | 0.00005 |
| SOLIDS ASH | 0.0002 |

TO LAND

Figure 1. (Continued)

1975b). A more recent EPA-sponsored study (1977c) of ambient surface waters collected from 204 sites near heavily industrialized areas across the United States identified DCE in 53 of the samples (26% of total). The reported values ranged from 1 ppb (detection limit) to 90 ppb (Delaware River site) (U.S. EPA, 1977c).

Data available in 1975 estimate that the atmospheric half-life of DCE is 3-4 months (U.S. EPA, 1975c). The stability estimate is based on the reaction of DCE with free hydroxy radicals. Subsequent to the formulation of this half-life estimate, the projected atmospheric concentration of hydroxyl radicals was revised downward. This would imply a longer atmospheric lifetime for DCE than formerly estimated. The expected major products of the reaction between DCE and hydroxyl radicals are monochloroacetyl chloride, hydrogen chloride, and monochloroacetic acid (U.S. EPA, 1975c).

1,2-Dichloroethane is slightly lipophilic in biological systems and thus has a slight tendency to bioaccumulate in the fat. However, bioaccumulation appears to be minimal (U.S. EPA, 1977b).

## REFERENCES

Brem, Henry et al. The mutagenicity and DNA-modifying effect of haloalkanes. Cancer Res. 34:2576, 1974.

Condensed Chemical Dictionary (CCD), 9th ed. New York, Van Nostrand Reinhold Co. 1977.

Ehrenberg, L. et al. On the reaction kinetics and mutagenic activity of methylating and β-halogenoethylating gasoline additives. Radiat. Bot. 15:185, 1974.

Gleason, M. N. et al. Clinical Toxicology of Commercial Products. Baltimore, Williams and Wilkins Co. 1969.

Gothe, R. et al. Trapping with 3,4-dichlorobenzenethiol of reactive metabolites formed in vitro from the carcinogen vinyl chloride. Ambio 3:234, 1974. (As cited in McCann et al., 1975)

Hardie, D. W. F. Chlorocarbons and chlorohydrocarbons. In Kirk-Othmer Encyclopedia of Chemical Technology, vol. 5. New York, Interscience Publishers. 1967. p. 149.

Heppel, L. A. et al. Toxicology of dichloroethane: I. Effect on the cornea. AMA Arch. Ophthalmol. 32:391, 1944. (As cited in Irish, 1963)

Heppel, L. A., and V. T. Porterfield. Enzymic dehalogenation of certain brominated and chlorinated compounds. J. Biol. Chem. 176:763, 1948. (As cited in McCann et al., 1975)

Irish, D. D. Halogenated hydrocarbons: I. Aliphatic. In F. A. Patty (ed.), Industrial Hygiene and Toxicology, vol. II. New York, Interscience Publishers. 1963. p. 1280.

Jensen, S. et al. On the chemistry of EDC-tar and its biological significance in the sea. Proc. R. Soc. London Ser. B 189: 333, 1975.

Lawrence, W. H. et al. Toxicity profile of chloroacetaldehyde. J. Pharm. Sci. 61:19, 1972. (As cited in McCann et al., 1975)

Lawenheim, Frederick A., and Marguerite K. Moran. Faith, Keyes, and Clark's Industrial Chemicals, 4th ed. New York, John Wiley and Sons. 1975. p. 392.

Malaveille, C. et al. Mutagenicity of vinyl chloride, chloroethylene oxide, chloroacetaldehyde, and chloroethanol. Biochem. Biophys. Res. Commun. 63:363, 1975. (As cited in McCann et al., 1974)

McCann, Joyce et al. Mutagenicity of chloroacetaldehyde, a possible metabolic product of 1,2-dichloroethane (ethylene dichloride), chloroethanol (ethylene chlorohydrin), vinyl chloride and cyclophosphamide. Proc. Natl. Acad. Sci. U.S.A. 72(8): 3190, 1975.

NIOSH (National Institute of Occupational Safety and Health). Criteria for a Recommended Standard. Occupational Exposure to Ethylene Dichloride. 1976.

Olson, W. A. et al. Induction of stomach cancer in rats and mice with halogenated aliphatic fumigants. J. Natl. Cancer Inst. 51(6):1993, 1973.

Rapoport, I. S. Reaction of gene proteins with ethylene chloride. Akad. Nauk. SSSR Dokl. Biol. Sci. 134:745, 1960. (As cited in McCann et al., 1975)

Rosenbaum, N. D. Ethylene dichloride as an industrial poison. Gig. Sanit. 12(2):17, 1947. (As cited in NIOSH, 1976)

Rosenkranz, S. et al. 2-Haloethanols: Mutagenicity and reactivity with DNA. Mutat. Res. 26:367, 1974. (As cited in McCann et al., 1975)

Shakarnis, V. F. Induction of X-chromosome nondisjunction and recessive sex-linked lethal mutations in females of Drosophila melanogaster by 1,2-dichloroethane. Genetica 5:89, 1969. (As cited in McCann et al., 1975)

SRI. (Stanford Research Institute). Chemical Economics Handbook. Menlo Park, Calif. 1975.

Urosova, T. P. About a possibility of dichloroethane absorption into milk of nursing women when contacted under industrial conditions. Gig. Sanit. 18:36, 1953. (As cited in NIOSH, 1976)

U.S. Environmental Protection Agency (U.S. EPA). Assessment of Ethylene Dichloride as a Potential Air Pollution Problem, vol. III. 1975a.

U.S. Environmental Protection Agency. Draft Report for Congress: Preliminary Assessment of Suspected Carcinogens in Drinking Water. 1975b. (As cited in EPA, Potential Industrial Carcinogens and Mutagens, EPA 560/5-77-005, 1977)

U.S. Environmental Protection Agency. Report on the Problem of Halogenated Air Pollutants and Stratospheric Ozone. ESRL-ORD, EPA 600/9-75-008, 1975c.

U.S. Environmental Protection Agency. Scoring of Organic Air Pollutants: Chemistry, Production and Toxicity of Selected Synthetic Organic Chemicals. 1976a.*

U.S. Environmental Protection Agency. Assessment in Industrial Hazardous Waste Practices, Organic Chemicals, Pesticides and Explosives. 1976b.

U.S. Environmental Protection Agency. A Study of Industrial Data on Candidate Chemicals for Testing. EPA 560/5-77-006, 1977a.

U.S. Environmental Protection Agency. Review of the Environmental Fate of Selected Chemicals. EPA 560/5-77-003, 1977b.

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*This document was prepared for the U.S. Environmental Protection Agency by the MITRE Corp. It is a secondary source and does not cite its primary references. Thus, verification of some information is not possible. The environmental release data were taken from NSF/Rann Research Program on Hazard Priority Ranking of Manufacturing Chemicals.

U.S. Environmental Protection Agency. Monitoring to Detect Previously Unrecognized Pollutants in Surface Waters. EPA 560/6-77-015, 1977c.

U.S. International Trade Commission. Synthetic Organic Chemicals. 1969, 1971, 1973, 1974, 1975.

Voogd, C. E. et al. On the mutagenic action of dichlorovos. Mutat. Res. 16:413, 1972. (As cited in McCann et al., 1975)

Voogd, C. E. Mutagenic action of epoxy compounds and several alcohols. Mutat. Res. 21:52, 1973. (As cited in McCann et al., 1975)

Yllner, S. Metabolism of 1,2-dichloroethane-$^{14}C$ in the mouse. Acta Pharmacol. Toxicol. 30:257, 1971. (As cited in McCann et al., 1975)

Zief, M., and C. H. Schramm. Chloroethylene oxide. Chem. Ind. 16:660, 1964. (As cited in McCann et al., 1975)

# CHEMICAL HAZARD INFORMATION PROFILE

## N,N-dimethylformamide

Date of report: April 13, 1978

This chemical was chosen for study because of the exposure potential associated with its use as a solvent and because of an inquiry regarding its health effects.

The following recommendations are made regarding further OTE evaluation of the possible health or environmental hazards of N,N-dimethylformamide (DMF):

(1) Check TSCA inventory for production volume--Good production figures are not currently available.

(2) Consider need for testing--The use patterns of DMF along with its potential for a greatly increased market imply a potential for widespread exposure. Also, the results of teratogenicity studies performed to date are somewhat conflicting.

(3) Require Section 8(a) submission--Determine the extent to which DMF is used in consumer products.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

### Chemical Identity

N,N-dimethylformamide is a liquid which boils at 153°C and has a vapor pressure of 3.7 mm Hg. It is infinitely soluble in water, alcohol, and ether (Weast, 1971; MITRE Corp., 1976).

### Production and Use

Dimethylformamide (DMF) is produced commercially by reacting dimethylamine and methyl formate (Louderback, 1965). Production figures for DMF itself could not be found because there are only two producers (U.S. ITC, 1975). However, the EPA Organic Chemical Producer's Data Base does contain data on DMF production. In 1972, SRI estimated that about half the dimethylamine produced was used for the manufacture of DMF and dimethylacetamide; 96 million lb of dimethylamine was produced in 1972.

Dimethylformamide is a polar, relatively nonvolatile solvent used in the manufacture of films, fibers, adhesives, and coatings. Examples of polymer products made in this solvent are polyacrylonitrile fibers, polyvinyl chloride, urethane fabric coatings, and Orlon . DMF is a component in paint strippers and is a solvent for pigments of low solubility. These pigments include azo dyes and nitroso compounds and are used in textiles, paper, and plastics. Antifreeze gasoline additives contain small quantities of DMF. DMF is used as a selective extractant in the purification of oils and gases and is also used as catalyst and intermediate in the production of acetals, aldehydes, esters, and other compounds (Louderback, 1965).

## Health Aspects

Single exposures to dimethylformamide are not particularly hazardous, but irreversible systemic damage can occur when DMF is inhaled or absorbed through the skin over a period of time (Louderback, 1965).

DMF has low acute oral toxicity; the rat oral $LD_{50}$ is 4,200 mg/kg. Central nervous system toxicity was reported in humans who inhaled concentrations of 20 ppm (NIOSH, 1975). In a case of acute occupational exposure involving both inhalation and dermal exposure, DMF caused severe abdominal pain and hepatic abnormalities. Disturbed porphyrin metabolism was suggested as a possible mechanism; other symptoms included anorexia, vomiting, dermal irritation, hypertension, and weakness (Potter, 1973).

Among workers exposed to DMF, allergic gastritis and dermatitis have been reported (DiLorenzo and Grazioli, 1972). DMF enhances skin penetration (Wiles and Narcisse, 1971), so precautions are normally taken to avoid skin contact. In a fiber plant where DMF, methyl methacrylate, and acrylonitrile were present, workers complained of skin and nervous system disorders (Stamova et al., 1976). Workers have also noted headaches and a flushed feeling after drinking alcohol; there is evidence that ethanol alters DMF metabolism in rats (Hanasono et al., 1977).

Several Russian scientists have done experiments which attempt to measure chronic health effects of nonoccupational exposure to DMF. Measurable quantities of DMF were present in underwear made from polyacrylonitrile fibers. Aqueous extracts from the cloth produced no changes in blood or liver functions in 4 months in animals exposed dermally (Rapoport et al., 1974). Shoes made from unstable polymers allowed both DMF and styrene to migrate through the skin (Es'Kova Soskovets, 1973).

Carnaghan (1967) reports that no tumors were observed after 32 months in 19 rats. DMF was administered once by gastric intubation.

DMF can cross the placenta and does accumulate in the fetus of rats (Sheveleva et al., 1977). DMF was applied to the skin of pregnant rabbits during fetal organogenesis; no teratogenic effects were seen, but slight embryotoxicity was noted (Stula and Krauss, 1977). DMF was reported as not teratogenic to chick embryos (reference unknown). Pregnant rats exposed via inhalation produced normal fetuses; however, high doses led to a weight loss in the fetus (Kimmerle and Machemer, 1975). Repeated doses of DMF were teratogenic for mice; no other details were given (Scheufler, 1976).

Although the mechanism of DMF metabolism is not understood, it is known that the majority of DMF is eliminated within 24 hr in humans (Kimmerle and Eben, 1975). To estimate total exposure to DMF, the concentration of DMF and its metabolites, monomethylformamide and formamide, in the urine may be measured (Barnes and Henry, 1974). Dogs exposed chronically to 10 ppm did not accumulate DMF (Kimmerle and Eben, 1975). The TLV for DMF is 10 ppm (ACGIH, 1971).

## Environmental Aspects

Dimethylformamide has been found in Polish industrial wastewater; it is not known to what extent industrial effluents are a problem domestically (Dojlido, 1977). Due to its infinite solubility in water, DMF does present a water treatment problem. Romadina (1975) and Begert (1974) report that DMF can be biodegraded by bacteria. At high DMF concentrations, though, the bacteria are poisoned (Begert, 1975).

Dimethylformamide is listed in EPA's Chemical Spills File and would be considered a hazardous material in the event of an accidental spill.

## REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). Cincinnati, Ohio. 1971.

Barnes, J. R., and N. W. Henry. The determination of N-methyl formamide and N-methyl acetamide in urine. Am. Ind. Hyg. J., p. 84, February 1974.

Begert, A. Biological purification of dimethylformamide-containing industrial sewage. Von Wasser 43:403, 1974.

Begert, A. Purification of chemical textile plant sewage. Oesterr. Abwasser-Rundsch. 20:98, 1975. (Abstract)

Carnaghan, R. B. A. Br. J. Cancer 21:811, 1967. (Cited in PHS 149)

DiLorenzo, F., and C. Grazioli. Hematologic, hematochemical and gastric function findings in workers exposed to inhalation of dimethylformamide vapor. Lav. Um. 24(4):97, 1972. (Abstract)

Dojlido, J. Testing of biodegradability and toxicity of organic compounds in industrial wastewaters. U.S. Environmental Protection Agency. Polish/U.S. Symp. Wastewater Treat. Sludge Disposal. 1977. p. 122.

Es'Kova-Soskovets, L. B. Biological effect of chemical substances migrating from shoes during their wearing. Gig. Sanit. 38: 101, 1973. (Abstract)

Hanasono, G. K., R. W. Fuller, W. D. Broddle, and W. R. Gibson. Studies on the effects of N,N'-dimethylformamide on ethanol disposition and monoamine oxidase activity in rats. Toxicol. Appl. Pharmacol. 39:461, 1977.

Kimmerle, B., and A. Eben. Metabolism studies of N,N-dimethylformamide: II. Studies in persons. Int. Arch. Arbeitsmed. 34(2):127, 1975. (Abstract)

Kimmerle, G., and L. Machemer. Studies with N,N-dimethylformamide for embryotoxic and teratogenic effects on rats after dynamil inhalation. Int. Arch. Arbeitsmed. 34(3):167, 1975. (Abstract)

Llewellyn, G. C., W. S. Hastings, and T. D. Kimbrough. The effects of dimethylformamide on female mongolian gerbils, Reriones ungulculatus. Bull. Environ. Contam. Toxicol. 11(5):467, 1974.

Louderback, H. Kirk-Othmer Encyclopedia of Chemical Technology, 2nd ed., vol. 10. New York, John Wiley and Sons. 1965. p. 109.

MITRE Corp. Scoring of Organic Air Pollutants. Chemistry, Production, and Toxicity of Selected Synthetic Organic Chemicals. 1976.

NIOSH. Registry of Toxic Effects of Chemicals, 1975 ed.

Potter, H. Phelps. Dimethylformamide-induced abdominal pain and liver injury. Arch. Environ. Health 27:340, 1973.

Rapoport, K. A., S. F. Ionkina, and L. A. Mintseva. Hygienic evaluation of underwear made of polyacrylonitrile fibers and their mixtures with natural fiber. Gig. Sanit. 12:85, 1974. (Abstract)

Romadina, E. S. Direct action of microorganisms. Biol. Samoochish-Chemie 2nd, 110, 1975. (Abstract)

Scheufler, H. Experimental testing of chemical agents for embryotoxicity, teratogenicity, and mutagenicity. Biol. Rundsch. 14(14):227, 1976. (Abstract)

Schottek, W. Experimental animal studies on the toxicity of dimethylformamide under repeated use. Acta Biol. Med. Ger. 25(2):359, 1970. (Abstract)

Sheveleva, G. A., O. V. Sivochalova, S. A. Osina, and L. S. Sal'nikova. Permeability of placenta to dimethylformamide. Akush. Ginekol. 5:44, 1977. (Abstract)

Stamova, N., N. Ginceva, M. Spasovski et al. Labor hygiene during the production of Bulana synthetic fibers. Khig. Zdraveopaz. 19(2):134, 1976. (Abstract)

Stanford Research Institute (SRI). Chemical Economics Handbook. Menlo Park, Calif. 1975.

Stula, E. F., and W. C. Krauss. Embryotoxicity in rats and rabbits from cutaneous application of amide-type solvents and substituted ureasP. Toxicol. Appl. Pharmacol. 41(1): 35, 1977. (Abstract)

Tanka, K. I. Toxicity of dimethylformamide to the young female rat. Int. Arch. Arbeitsmed. 78(2):96, 1971. (Abstract)

Ungar, H., S. F. Sullman, and A. J. Zuckerman. Acute and protracted changes in the liver of Syrian hamsters induced by a single dose of aflatoxic F1'. Br. J. Exp. Pathol. 57(2):157, 1976. (Abstract)

U.S. International Trade Commission. Synthetic Organic Chemicals, United States Production and Sales. 1975.

Weast, Robert C. (ed.). CRC Handbook of Chemistry and Physics, 52nd ed. Cleveland, The Chemical Rubber Co. 1971.

Wiles, J. S., and J. K. Narcisse. The acute toxicity of dimethylamides in several animal species. Am. Ind. Hyg. Assoc. J. 32(8):539, 1971. (Abstract)

# CHEMICAL HAZARD INFORMATION PROFILE

## Dinitrosopentamethylenetetramine

Date of report: June 1, 1978

This chemical was chosen for study because of worker complaints received by OSHA. Workers at a dinitrosopentamethylenetetramine (DNPT) plant complained of fainting, dizziness, cyanosis, and convulsions.

It is recommended that judgment on DNPT be deferred until OSHA completes its report on occupational health problems associated with the chemical. The OSHA study should provide a much better characterization of the problem than is currently available. This CHIP should be updated based on the additional information obtained.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

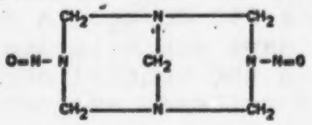
Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

## Chemical Identity

Synonyms: DNPT; 3,7-dinitroso-1,3,5,7-tetraazabicyclononane

CAS No.: 101-25-7

A structural diagram of DNPT is shown below:



DNPT is a light-yellow solid which decomposes at 207°C. When used with rubber or plastics, its decomposition temperature is lowered to 130-190°C. It is slightly soluble in water, alcohol, and benzene, and dissolves readily in dimethylformamide (IARC; 1976; McCaleb, 1978).

## Production and Use

IARC reports U.S. consumption of DNPT at 3 million lb in 1970. SRI estimates annual production at 2-3 million lb. The U.S. ITC (1975) reports one producer, Stepan Chemical Co.

DNPT is used as a blowing agent in rubbers and plastics. Natural and synthetic unicellular rubber, which is made using DNPT, is used as carpet underlay, weatherstripping, insulation, shoe lining, and cushioning. DNPT is also an effective blowing agent for polyvinyl chloride plastisols and epoxy, polyester, and silicone resins.

DNPT is produced from hexamine (hexamethylenetetramine), HCl, and sodium nitrite. During its use as a blowing agent, acidic substances such as phthalic anhydride and ethylene glycol are often added to accelerate the reaction and to lower the temperature of the decomposition process. Decomposition products are not fully elucidated; possible ones are amines, water, nitrous oxide, nitrogen gas, formaldehyde, and ammonia. A fishy odor, due to the amines, and the high decomposition temperature make DNPT an unsuitable blowing agent for many plastics, though it is the most widely used blowing agent for rubber sponges (McCaleb, 1978).

## Health Aspects

The chemical was referred to us by OSHA (Stewart, 1978), which is investigating complaints of fainting, dizziness, cyanosis, and convulsions at a DNPT production plant. All ten workers reported one or more symptoms. An OSHA medical team plans to carefully inspect the plant during the week of May 30, 1978.

No health effects information was found aside from the IARC report, which is summarized below.

The rat oral $LD_{50}$ was 940 mg/kg. A dose of 80 mg/kg injected intraperitoneally for 30 days was tolerated. Higher doses produced toxic effects within the central nervous system, including depression of conditioned reflexes and tonic and clonic spasms (Desi et al., 1967).

No tumors were induced in female rats given a single oral dose of 90 mg DNPT within 6 months (Griswold et al., 1966), nor were tumors induced after 18 months in 15 male and 15 female rats given 9 mg DNPT by oral gavage daily for 1 year (Weisburger et al., 1966). Rats fed 0.03, 1, 3, or 9 mg DNPT 4 days/week for a year did not have an increased tumor incidence after 18 months (Hadidian et al., 1968).

Boyland et al. (1968) reported that of 24 male rats given weekly IP injections of 25 mg DNPT for 26 weeks, 13 survived over 16 months. One developed a hepatoma and another developed a pituitary tumor. However, one of the controls developed a hepatoma, and IARC concluded that DNPT is not a rat carcinogen by oral administration or by intraperitoneal injection.

## Environmental Aspects

No information was found in the sources consulted on environmental fate or effects of DNPT.

## REFERENCES

Boyland, E. et al. Carcinogenic properties of certain rubber additives. Eur. J. Cancer 4:233, 1968.

Desi, F. et al. Investigations on the nervous effects of N,N-dinitrosopentamethylenetetramine (Mikrofor) in rats. Med. Lav. 58:22, 1967.

Griswold, P. P. et al. On the carcinogenicity of a single intragastric dose of hydrocarbons, nitrosamines, aromatic amines, dyes, coumarins, and miscellaneous chemicals in female Sprague-Dawley rats. Cancer Res. 26:619, 1966.

Hadidian, Z. et al. Tests for chemical carcinogens. J. Natl. Cancer Inst. 41:985, 1968.

International Agency for Research on Cancer (IARC). Evaluation of Carcinogenic Risk of Chemicals to Man, vol. 11. 1976. p. 241.

McCaleb, Kirt, at SRI International, Menlo Park, Calif., personal communication, May 18, 1978.

Stewart, Trish, OSHA, personal communication, May 18, 1978.

U.S. International Trade Commission (U.S. ITC). 1975.

Weisburger, J. H. et al. New carcinogenic nitrosamines. Naturwissenschaften 53:508, 1966.

## Bibliography

Encyclopedia of Polymer Science and Technology, vol. 2, Blowing Agents (Chapter) has a few pages on DNPT.

Reed, R. A. Plastic progress. London, Iliffe and Sons Ltd. 1955. p. 51-80.

R. A. Br. Plast. 33(10):469, 1969.

Rubber Age, February 1976, p. 22.

Rubber World Blue Book 1975. Useful for trade names.

# CHEMICAL HAZARD INFORMATION PROFILE

## 2,4-Dinitrotoluene

Date of report: March 9, 1978

This chemical was chosen for study because of a determination of its carcinogenicity in an NCI bioassay.

If the contractor report on nitroaromatics does not provide adequate use information on 2,4-dinitrotoluene, TSCA Section 8(a) submissions should be required. Use information will be necessary for exposure estimates. A revised Chemical Hazard Information Profile should be prepared when satisfactory use information is obtained.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

### Chemical Identity

2,4-Dinitrotoluene ($C_7H_6N_2O_4$) exists as yellow crystalline needles at room temperature. Its melting range is from 69.5 to 70.5°C. 2,4-Dinitrotoluene (2,4-DNT) decomposes at 300°C. Its molecular weight is 182.1, and its density is 1.521 (at 15°C). 2,4-DNT is sparingly soluble in water (0.027 g/100 ml at 22°C) and is soluble in ether and in alcohol. Synonyms for 2,4-DNT (CAS No. 121-14-2) include 2,4-dinitrotoluol and 1-methyl-2,4-dinitrobenzene. 2,4-DNT is considered a moderate fire and explosion risk. It can be detonated only by a strong initiator but may become an explosion hazard when involved in fire (Sax, 1968).

### Production and Use

Dinitrotoluene can be produced by batch or continuous process. The starting material is usually 2- or 4-nitrotoluene, although toluene itself is sometimes used. The dinitrotoluene resulting from use of 2-nitrotoluene will contain both the 2,4- and 2,6-isomers. The continuous process may consist of several reactors joined in series. The raw materials (toluene/nitrotoluene and an acid mixture of $H_2SO_4$ and $HNO_3$) are added only to the first reactor. Successive chambers provided additional reaction time. This exothermic reaction has an overall yield of roughly 96%. The acid is then removed. The crude dinitrotoluene is washed and neutralized. Most of the product that is formed goes directly to a reduction step, forming diaminotoluene; however, some material may be distilled if high-purity 2,4-dinitrotoluene is needed (EPA, 1976).

Shipping solids, such as 2,4-DNT, in a molten state in tank cars is a common practice. The price of 2,4-DNT was 22.5¢/lb (in tanks) in 1975 (EPA, 1976).

Manufacture of toluene diisocyanate consumes much of the 2,4-DNT produced. In 1976, 560 million lb of toluene diisocyanate was produced. This production consumed roughly 389 million lb of toluene (SRI, 1976). A total of 389 million lb of toluene would produce approximately 740 million lb of 2,4-DNT, assuming 96% yield (U.S. EPA, 1976). 2,4-DNT is also used as a gelatinizing and waterproofing agent in explosives and as a dye intermediate (SRI, 1976).

U.S. DNT production

| Year | Substance | Pounds produced |
|---|---|---|
| 1971 | 2,4- (and 2,6-) DNT | 352,746,000 |
| 1972 | 2,4- (and 2,6-) DNT | 433,885,000 |
| 1973 | 2,4- (and 2,6-) DNT | 471,237,000 |
| 1974 | 2,4- (and 2,6-) DNT | 522,842,000 |
| 1975 | 2,4-DNT | 308,257,000 |
|  | 2,4- (and 2,6-) DNT | 272,610,000 |

Source: U.S. ITC, 1973-77.

Based upon the growth projections for the major uses of DNT, demand should increase by 6.5 to 7.5% per year (EPA, October 1977).

2,4-DNT is produced by Air Products & Chemicals, Inc., Pensacola, Fla., and by Rubicon Chemicals, Inc., Geismar, La. 2,4- (and 2,6-) DNT is produced by E. I. du Pont, Deepwater, N.J., and by Mobay Chemicals Corp., Cedar Bayou, Tex., and New Martinsville, W. Va. (SRI, 1975). Other companies may manufacture 2,4-DNT as a chemical intermediate for captive use.

## Health Aspects

The TLV (and TWA) of 2,4-DNT is 1.5 mg/m$^3$ (air). It may be absorbed through intact skin. Symptoms of DNT exposure include headache, vertigo, fatigue, shortness of breath, anorexia, palpitation, arthralgia, insomnia, tremor, and paralysis (ITII, 1976). Advanced cases show symptoms such as jaundice and secondary anemia (ACGIH, 1971).

Exposure of rats to 50 mg/kg 2,4-DNT (orally) or to 200 ppm 2,4-DNT (1-hr inhalation) produced no mortality. The oral $LD_{50}$ is 268 mg/kg for rats and 1,625 mg/kg for mice. There is evidence that a high-fat, low-protein diet renders rats more susceptible to TNT and DNT poisoning. Application of 200 mg/kg to the skin of rabbits did not cause mortality, nor was it corrosive to the skin. The $LD_{50}$ for oral administration of 2,4-DNT to cats is 27 mg/kg (EPA, 1976). NCI has conducted a bioassay of 2,4-DNT. It was fed to rats at 0.02% or 0.008% of their diet. Both levels increased the incidence of fibroma of the skin and subcutaneous tissue in male rats. The high dose caused a statistically significant incidence of fibroadenoma of the mammary gland in female rats. Mice fed 0.04% or 0.008% 2,4-DNT did not show tumors which could be attributed to the compound. NCI considers the results of this bioassay to be positive.

## Environmental Aspects

The aquatic toxicity rating of 2,4-DNT is 100 to 10 ppm for 96 hr of exposure (NIOSH, 1976). 2,4-DNT depressed or killed colonies of *Lemna perpusilla* (an aquatic flowering plant) at concentrations of 1 ppm and above.

Nitroaromatics are, generally, very stable in water under neutral conditions. 2,4-DNT is an o-alkyl nitroaromatic compound, and therefore is probably susceptible to photochemical alteration since such compounds isomerize to highly colored compounds which may react further (EPA, 1976).

EPA has identified 2,6-DNT in drinking water. Kite (1961) detected 2,4-DNT in the red water wastes from a TNT plant (Picatinny Arsenal, Dover, N.J.) by using solvent extraction, column chromatography, and infrared spectrometry. Investigators have found DNT in the wastewater effluents of other TNT plants and in the plant, the raw wastes, and the pond effluent of an explosives plant (EPA, 1976).

Biodegradation experiments conducted using microorganisms in soil, compost, or moved from a catalytic cracking plant waste lagoon, adapted to phenol, showed that the ratio of the test oxygen uptake rate to the endogenous rate was nearly 2.5 for 2,4-DNT. This implies that it is biodegradable to some degree. In another study, Soviet scientists estimated that 95 to 97% of 2,4-DNT was removed after the second stage of activated sludge digestion (EPA, 1976). Enriched pure soil culture will slowly/partially degrade 2,4-DNT in soil.

Most of the DNT produced is used captively. However, based on the presence of DNT in sewage wastes from TNT and explosives manufacturing plants, environmental and water supply contamination seems to be a distinct possibility.

## REFERENCES

American Conference of Governmental Industrial Hygienists (ACGIH). Documentation of the Threshold Limit Values, 3rd ed. 1971.

International Technical Information Institute (ITII). Toxic and Hazardous Industrial Chemicals Safety Manual. Tokyo. 1976.

Kite, D., Jr. Air and stream pollution control: Preliminary survey of thermal methods for trinitrotoluene red water disposal. 1961. (As cited in U.S. EPA, 1976)

NIOSH. Registry of Toxic Effects of Chemical Substances, 1976 ed.

Sax, N. Irving. Dangerous Properties of Industrial Materials. New York, Van Nostrand Reinhold Co. 1968.

Stanford Research Institute (SRI). Directory of Chemical Producers. Menlo Park, Calif. 1975.

SRI. Chemical Economics Handbook. Menlo Park, Calif. 1976.

U.S. Environmental Protection Agency (U.S. EPA). Investigation of Selected Potential Environmental Contaminants: Nitroaromatics. June 1976.

U.S. Environmental Protection Agency. Information Profiles on Potential Occupational Hazards. October 1977.

U.S. International Trade Commission (U.S. ITC). Synthetic Organic Chemicals, U.S. Production and Sales, 1973-1977.

# CHEMICAL HAZARD INFORMATION PROFILE

## Ethanolamines

Date of report: April 14, 1978

This group of chemicals was chosen for study because of the potential for nitrosamine contamination.

The following recommendations are made regarding further OTE evaluation of the possible health or environmental hazards of ethanolamines:

(1) Proceed to Phase I report--Potential problems with substances containing ethanolamines are sufficiently serious and sufficiently characterized to warrant further assessment.

(2) Require Section 8(a) submissions--Quantitative information on use patterns will better define the exposure profile.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

### Chemical Identity

Ethanolamines have a low vapor pressure; triethanolamine and diethanolamine are white solids, while monoethanolamine is a clear liquid. These compounds are miscible in water and alcohol and insoluble in ether (Hart, 1967).

### Production and Use

Ethanolamines are produced commercially by reacting aqueous ammonia with ethylene oxide. Annual production is as follows: monoethanolamine, 83 x $10^6$ lb; diethanolamine, 86 x $10^6$ lb; and triethanolamine, 89 x $10^6$.

The consumption pattern for these three compounds is similar. In the petroleum and natural gas industry, monoethanolamine and diethanolamine are used to remove acidic gases. Ethanolamines are used as emulsifiers and dispensing agents in a variety of cosmetics including cold cream and shaving cream. Ethanolamines are used in the manufacture of detergents for wool manufacture, drycleaning, cosmetics, and household use. As surface-active ingredients, ethanolamines are used in the manufacture of waxes, polishes, and cutting fluids. Some fruit-ripening agents contain a mixture of ethanolamines, and they are also used to solubilize herbicides. Finally, ethanolamines are used as intermediates in the production of morpholine, resins, and plasticizers (Hartung and Cornish, 1968; SRI, 1975).

## Health Aspects

Ethanolamines are generally considered to have low acute toxicity. The oral $LD_{50}$ values for rats are (NIOSH, 1976): monoethanolamine, 2,100 mg/kg; diethanolamine, 710 mg/kg; and triethanolamine, 8,680 mg/kg.

However, ethanolamines are irritating, and triethanolamine may be sensitizing to the skin and mucous membranes (Lopukhova, 1964).

An occupational standard has been set only for monoethanolamine. The TLV is 3 ppm (ACGIH, 1971).

Ethanolamines are a normal constituent of human urine; they are metabolized rapidly and are ultimately incorporated into the phospholipids of the liver and kidney (Taylor and Richardson, 1967). There is one known occupational case of acute poisoning by monoethanolamine in which toxic liver damage and chronic hepatitis occurred (Jindrichova and Urban, 1971). In subacute rodent feeding studies, all three compounds induced liver and kidney weight changes, and diethanolamine caused fatty degeneration of the liver (Sutton, 1963; Hartung and Cornish, 1968). Other pathological changes included inhibition of cholinesterase by all ethanolamines (Hartung and Cornish, 1968).

Bose (1972) showed that triethanolamine induced meiotic irregularities in onion cells. However, in another study (SRI, 1977) monoethanolamine did not affect meiosis in onions and did not induce point mutations in a bacterial species. SRI experts do not believe that either of these systems has been adequately characterized as a screen for mammalian gene damage.

An industry study showed that hair dye with a base containing 22% monoethanolamine did not increase the incidence of birth defects in dogs, rabbits, or rats. The rats and dogs were exposed orally, and the rabbits by gavage (Wernick et al., 1975).

Kostrodymova et al. (1976) reported that a triethanolamine solution was not carcinogenic to rats exposed via the skin; no other details were given. Grinding fluid containing triethanolamine and sodium nitrite at gastric pH formed N-nitrosodiethanolamine (Zingmark and Rappe, 1976). Druckery et al. (1963) fed nitrosodiethanolamine intermittently to rats for 41 weeks, and all developed liver cancer. N-nitrosodiethanolamine has been found at levels as high as 48 ppm in cosmetics and toiletry products (C&E News, 1977). Enviro Control Inc. has a contract with NIOSH to study the carcinogenic effects of hydraulic and cutting fluids which contain diethanolamine and nitrite (Tox-tips, November 1977).

## Environmental Aspects

The MITRE Corp. (1976) reports an annual environmental release rate for diethanolamine and triethanolamine as 36 million lb for each compound.

The aquatic toxicity ratings indicate that diethanolamine is an "insignificant hazard" and that monoethanolamine and triethanolamine are "practically nontoxic" (NIOSH, 1976).

Apostol (1975) reports that he first noted acute effects in aquatic organisms at 100 mg/l and chronic effects at 1 mg/l. The most sensitive organisms were daphnia, ciliated protozoa, and amoeba.

## REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). Documentation of Threshold Limit Values. Cincinnati, Ohio. 1971.

Apostol, S. Ethanolamine toxicity to aquatic invertebrates. Stud. Cercet. Biol. 27(4):345, 1975. (Cited in Chem. Abstr. 85:73051G)

Bose, S. Preliminary studies on triethanolamine induced meiotic irregularities in onion (*Allium cepa L.*) Sci. Cult. 38(3): 146, 1972.

C & E News. N-nitrosoamines found in toiletry products. March 28, 1977.

Druckrey, H., R. Preussmann, and D. Schmahl. Carcinogenicity and chemical structure of nitrosamines. Acta. Un. Int. Cancer 19(3-4):510, 1963.

Hart, A. W. Alkanolamines. *In* Kirk-Othmer Encyclopedia of Chemical Technology, vol. 1. 1967. p. 810-824.

Hartung, R., and H. H. Cornish. Cholinesterase inhibition in the acute toxicity of alkyl-substituted 2-aminoethanols. Toxicol. Appl. Pharmacol. 128:486, 1968.

Jindrichova, J., and R. Urban. Acute monoethanolamine poisoning. Prac. Lek. 23(9):314, 1971. (Cited in HEEP 72:09648)

Kostrodymova, G. M., V. M. Voronin, and N. N. Kostrodymov. Toxicity from the complex action and the possibility of carcinogenic and cocarcinogenic properties of triethanolamine. Gig. Sanit. 3:20, 1976. (Cited in Chem. Abstr. 84:174886t)

Lopukhova, K. A. Current problems on the effect of synthetic detergents on the skin. Gig. Tr. Prof. Zabol. 8(12):38-42, 1964.

MITRE Corp. Scoring of Organic Air Pollutants. Chemistry, Production, and Toxicity of Selected Synthetic Organic Chemicals.* 1976.

NIOSH. Registry of Toxic Effects of Chemical Substances. 1976.

SRI (Stanford Research Institute). A Study of Industrial Data on Candidate Chemicals for Testing. EPA-560/5-77-006, August 1977. p. 3-179.

Sutton, W. L. Aliphatic and alicyclic amines. In F. A. Patty (ed.), Industrial Hygiene and Toxicology, 2nd ed. New York, Interscience Publishers. 1963.

Taylor, R. J., Jr., and K. E. Richardson. Ethanolamine metabolism in the rat. Proc. Soc. Exp. Biol. Med. 124(1):247, 1967.

Tox-tips. Notice of Research Project. November 1977.

U.S. ITC (U.S. International Trade Commission). Synthetic Organic Chemicals, United States Production and Sales, 1975.

Wernick, T., B. M. Lanman, and J. L. Fraux. Chronic toxicity, teratologic, and reproduction studies with hair dyes. Toxicol. Appl. Pharmacol. 32(3): 450, 1975.

Zingmark, P. A., and C. Rappe. On the formation of N-nitrosodiethanolamine from a grinding fluid under simulated gastric conditions. Ambio 5(2): 80, 1976.

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*This document was prepared for the U.S. Environmental Protection Agency by the MITRE Corp. It is a secondary source and does not cite its primary references. Thus, verification of some information is not possible. The environmental release data were taken from NSF/Rann Research Program on Hazard Priority Ranking of Manufacturing Chemicals.

## CHEMICAL HAZARD INFORMATION PROFILE

## Ethylamines

Date of report: April 1, 1978

These chemicals were chosen for study because of their potential for being nitrosated and thereby forming nitrosamines. Certain nitrosamines are known carcinogens.

The following recommendations are made regarding further OTE evaluation of the possible health or environmental hazards of ethylamines:

(1) Refer to OSHA--Toxic effects have been seen in both humans and test animals at ethylamine concentrations below the current OSHA standard.

(2) Refer to OPP--Diethylamine was found as a degradation product of a commercial pesticide. This diethylamine was subsequently nitrosated to form diethylnitrosamine.

(3) Refer to the Office of Air Quality Planning and Standards--Significant amounts of amines may be released into the ambient air from manufacturing sites.

(4) Require Section 8(a) submission--Determine the presence of ethylamines in consumer products and revise this Chemical Hazard Information Profile accordingly.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

### Chemical Identity

Monoethylamine is a gas which condenses at 16.6°C. Diethylamine is a volatile liquid which boils at 55.5°C; triethylamine is also a liquid and boils at 89.3°C. All three compounds are soluble in water, have an ammoniacal odor, and are quite basic (MITRE Corp., 1976). The respective PKb and vapor pressure values (mmHg at 20°C) for these compounds are as follows: monoethylamine 3.36; diethylamine 3.39, 195; and triethylamine 3.29 and 53.5 (Sutton, 1963).

## Production and Use

In 1975, 12.4 million lb of diethylamine was produced. In the preceding year over 46 million lb of all ethylamines, excluding diethylamines, was manufactured. This figure may include some salts but should reflect the combined amount of monoethylamine and triethylamine manufactured in 1974 (U.S. ITC, 1974, 1975).

The ethylamines are used mostly as chemical intermediates for the production of pesticides, textile chemicals, medicinals, and corrosion inhibitors. Detailed breakdowns of use categories are not available, but some specific uses are listed below.

Monoethylamine (MEA) is used as an intermediate in the manufacture of the following chemicals: triazine herbicides, 1,3-diethylthiourea (a corrosion inhibitor), ethylaminoethanol, 4-ethylmorpholine (urethane foam catalyst), ethyl isocyanate, and dimethylolethyltriazone (agent used in wash-and-wear fabrics). The cuprous chloride salts of MEA are used in the refining of petroleum and vegetable oil.

Diethylamine (DEA) is used in the manufacture of the following chemicals: diethyldithiocarbamate and thiourams (rubber processing accelerators), diethylaminoethanol (medicinal intermediate) diethylaminopropylamine (epoxy curing agent), N,N-diethyl-m-toluamide (insecticide), and 2-diethylaminoethylmethacrylate.

Triethylamine (TEA) is used as a corrosion inhibitor in paint removers based on methylene chloride or other chlorinated solvents. TEA is used to solubilize 2,4,5-T in water and serves as a selective extractant in the purification of antibiotics. Octadecyloxymethyltriethylammonium chloride, an agent used in textile treatment, is manufactured from TEA (SRI, 1975).

## Health Aspects

Ethylamines produce strong local irritation when inhaled or on contact with the skin. Inhalation of small quantities of monoethylamine or triethylamine may cause death or permanent injury. Human effects are usually local; inhalation may cause eye irritation, lacrimation, conjunctivitis, nose and throat irritation, or coughing. Systemic symptoms such as headache, nausea, faintness, and anxiety may result from inhalation of ethylamines (Sax, 1975).

Rat oral $LD_{50}$ values are as follows; monoethylamine, 400 mg/kg; diethylamine, 540 mg/kg; and triethylamine, 460 mg/kg (NIOSH, 1975).

Brieger and Hodes (1951) exposed rabbits to 50 or 100 ppm ethylamines for 6 weeks. At the higher dose all three compounds produced degenerative changes in the liver, lungs, and kidneys. Only triethylamine weakened the heart. Eye irritation and slight liver damage were reported at the lower dose for each compound.

In a 5-year Russian study of children who lived near a factory which released monoethylamine, increases in acute respiratory, ear, and mastoid infections were noted. Additional changes reported were enhanced blood cholinesterase activity, disturbed porphyrin metabolism, and an elevated number of eye infections. The mean diurnal atmospheric concentration of MEA was 0.037 mg/m$^3$ (0.02 ppm), with a maximum of 0.293 mg/m$^3$ (0.16 ppm). In a 3-month study, rats were exposed to 3.69 mg/m$^3$ (2.0 ppm). A decrease in blood cholinesterase activity and changes in porphyrin metabolism were seen. A no-effect level was seen at 0.01 mg/m$^3$ (0.005 ppm) (Tkachev, 1969).

Hussain and Ehrenberg (1974) showed that a combination of monoethylamine and sodium nitrite is significantly more mutagenic than either compound alone. In this assay, E. coli mutated to streptomycin independence. Isakova et al. (1971) exposed rats to an ambient concentration of 1 mg/m$^3$ (0.25 ppm) triethylamine for 3 months. The number of rats having cells with an abnormal number of chromosomes in the bone marrow increased.

The major reason for our concern with ethylamine is that under conditions found in the digestive tract, diethylnitrosamine, an animal carcinogen, may be formed. Sodium nitrite and the HCl salt of diethylamine were incubated in human gastric juice (pH 1.2-1.9), and measurable amounts of diethylnitrosamine (DEN) were found. DEN was found in the stomachs of rabbits and cats who had been fed diethylamine and nitrite (Sen et al., 1969). Schweinsberg and Sander (1972) showed that nitrous acid and tertiary amines react to form nitrosamines, but much less is formed when compared to the corresponding secondary amine. In a 1-year feeding study, rats developed no tumors after exposure to both triethylamine and nitrite. Sander et al. (1968) showed that the amount of nitrosamine formed from a secondary amine depends on the basicity of that amine. Since the ethylamines are quite basic, one would expect a small amount of diethylnitrosamine to be formed. In a long-term feeding study, DEN produced liver tumors in 18 of 20 guinea pigs after 30 months. However, two groups fed combinations of diethylamine and nitrite suffered no ill effects other than weight loss (Sen et al., 1975).

The TLV values for occupational exposure in the U.S. are monoethylamine, 10 ppm; diethylamine, 25 ppm; and triethylamine, 25 ppm (ACGIH, 1971).

## Environmental Aspects

Monoethylamine is a normal constituent of human urine (Asatoor, 1969), and both monoethylamine and diethylamine are present in edible fish (Gruger, 1972). Little additional work has been done on the metabolism of ethylamines.

Normal commercial amounts of the pesticide diethyldithiocarbamate were converted to diethylamine in soil; measurable amounts of diethylnitrosamine were found (Tate and Alexander, 1974). Mosier (1974) showed that in a laboratory setting with pure water and no other organism, both MEA and DEA inhibit the growth of fresh-water algae. NIOSH's Aquatic Toxicity Rating ranks all three compounds as "slightly toxic."

## REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). Documentation of Threshold Limit Values. 1971.

Asatoor, A. M. Tea as a source of urinary ethylamine. Nature 210(5043):1358, 1969.

Brieger, H., and W. A. Hodes. Toxic effects of exposure to vapors of aliphatic amines. Arch. Ind. Hyg. Occup. Med. 3:287, 1951. (Cited in Sutton and PHS 149)

Gruger, E. H. Chromatographic analyses of volatile amines in marine fish. J. Agr. Food Chem. 20(4):781, 1972.

Hussain, S., and L. Ehrenberg. Mutagenicity of primary amines combined with nitrite. Mutat. Res. 26:419, 1974.

Isakova, G. K., B. Y. Ekshtat, and Y. Y. Kerkis. Mutagenic action of chemical substances in substantiation of hygienic standards. Gig. Sanit. 36(11):9, 1971.

MITRE Corp. Scoring of Organic Air Pollutants. Chemistry, Production, and Toxicity of Selected Organic Chemicals. 1976.*

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*This document was prepared for the U.S. Environmental Protection Agency by the MITRE Corp. It is a secondary source and does not cite its primary references. Thus, verification of some information is not possible. The environmental release data were taken from NSF/Rann Research Program on Hazard Priority Ranking of Manufacturing Chemicals.

Mosier, A. R. Effect of cattle feedlot volatiles, aliphatic amines, on Chlorella ellipoidea growth. J. Environ. Qual. 3(1):26, 1974.

NIOSH. Registry of Toxic Effects of Chemical Substances. 1975.

Sander, J., F. Schweinsberg, and H. Menz. Formation of carcinogenic nitrosamines in the stomach. Hoppe-Seyler's Z. Physiol. Chem. 349(12):1691, 1968.

Sax, N. I. Dangerous Properties of Industrial Materials, 4th ed. New York, Van Nostrand Reinhold. 1975.

Schweinsberg, F., and J. Sander. Carcinogenic nitrosamines from simple aliphatic tertiary amines and nitrite. Hoppe-Seyler's Z. Physiol. Chem. 353(11):1671, 1972.

Sen, N. P., D. C. Smith, and L. Schivenghamer. Formation of N-nitrosamines from secondary amines and nitrite in human and animal gastric juice. Food Cosmet. Toxicol. 7(4):301, 1969.

Sen, N. P. et al. Failure to induce tumors in guinea pigs after concurrent administration of nitrite and diethylamine. Food Cosmet. Toxicol. 13(4):423, 1975.

SRI (Stanford Research Institute). Chemical Economics Handbook. Menlo Park, Calif. 1975.

Sutton, W. L. Aliphatic and alicyclic amines. In F. A. Patty (ed.), Industrial Hygiene and Toxicology, 2nd ed. New York, Interscience Publishers. 1963.

Tate, R. L., and M. Alexander. Formation of dimethylamine and diethylamine in soil treated with pesticides. Soil Sci. 118(5): 317, 1974.

Tkachev, P. G. Monoethylamine in the atmosphere: Hygienic significance and standards. Gig. Sanit. 34(8):7, 1969.

U.S. ITC (U.S. International Trade Commission). Synthetic Organic Chemicals, U.S. Production and Sales, 1974 and 1975.

# CHEMICAL HAZARD INFORMATION PROFILE

## Ethylenediamine

Date of report: May 9, 1978

This chemical was chosen for study because of its presence in consumer products (pharmaceuticals) and its potential for nitrosamine formation.

The following recommendations are made regarding further OTE evaluation of the possible health or environmental hazards of ethylamines:

(1) Consider need for testing--Ethylenediamine is a relatively high-volume, high-exposure chemical with very limited information on toxicity.

(2) Require Section 8(a) submission--More specific information on uses is needed for exposure estimates.

(3) Refer to CPSC--Possibly present in products under CPSC's authority.

(4) Transmit to NIOSH on an FYI basis--NIOSH has scheduled a criteria document for aliphatic di- and polyamines.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendation based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

## Chemical Identity

Ethylenediamine (1,2-diaminoethane), $C_2H_8N_2$, is a colorless liquid (boiling point, 116-117°C) with an ammonia-like odor. It is soluble in water and alcohol, slightly soluble in ether, and insoluble in benzene (Hawley, 1971).

## Production and Use

Ethylenediamine is produced by heating ethylene dichloride and ammonia (Hawley, 1971). The 1978 Directory of Chemical Producers (SRI, 1978) lists the following manufacturers and plant capacities for ethylenediamine production:

|  | Annual capacity (millions of lb) |
|---|---|
| Dow Chem. U.S.A., Freeport, Tex. | 30 |
| Union Carbide Corp., Taft, La. | 39 |
| Chems. and Plastics Div., Texas City, Tex. | 24 |
| Total | 93 |

Ethylenediamine is used by the synthetic fiber manufacturing industry as a stabilizer in the production of caprolactam polymers (Wiithrich, 1972). It is used by the pharmaceutical industry as a stabilizer in aminophylline, which is used in antiasthmatic drugs, and in Mycolog , an antibiotic cream (Provost and Jillson, 1967).

Ethylenediamine is also used as a solvent stabilizer, as a neutralizer in rubber products, in dyes, waxes, dimethylolethylene-urea resins, fungicides, insecticides, and asphalt wetting agents, and in the manufacture of the chelating agent EDTA (Baer and Ramsey, 1973; Hawley, 1971).

## Health Aspects

Ethylenediamine's action as a contact allergen is well established. The North American Contact Dermatitis Group (1975) compiled results of skin patch tests conducted from July 1, 1972, to June 30, 1974. Six percent of the 3,216 patients tested exhibited sensitivity to 1% ethylenediamine-HCl solution. Baer and Ramsey (1973) reported patch tests performed on patients at the New York University Skin and Cancer Unit. A 1% solution of ethylenediamine elicited a positive response in 13.2% of the 158 patients tested.

Significant case studies involving ethylenediamine exposure include:

(1) A patient with a history of allergic reaction to Mycolog cream was treated with aminophylline suppositories following hospitalization for acute dyspnea. He developed a generalized exfoliative dermatitis. Both drugs contain ethylenediamine-HCl (Petrozzi and Shore, 1976).

(2) A patient who had handled epoxy resins and hardeners in an electrical appliance factory developed dermatitis following the use of Mycolog cream. Exposure to the Mycolog cream occurred 3 years after a 6-month exposure to the epoxy resins and hardeners. Two other patients developed dermatitis following repeated use of Mycolog cream. All three patients showed sensitivity to ethylenediamine in skin patch tests (Van Hecke, 1975).

The OSHA standard for workplace exposure to ethylenediamine is 10 ppm. This value is also the American Conference of Governmental Industrial Hygienists' threshold limit value.

## Environmental Aspects

The estimated release rate of ethylenediamine is 22.5 million lb per year. It is reactive toward atmospheric oxidants. The 20-day BOD is 70% of the theoretical value (Dorigan et al., 1976).

The 96-hr $LC_{50}$ for aquatic life (test species unknown) is 10-100 ppm (NIOSH, 1977).

Ethylenediamine is a degradation product of the agricultural fungicide maneb. A field study was conducted to determine levels of degradation products found on beans and tomatoes sprayed with maneb. Fourteen days after the final application of maneb, 0.09 ppm of ethylenediamine was found on beans and 0.05 ppm was found on tomatoes (Newsome et al., 1975).

## REFERENCES

Baer, R. L., and D. L. Ramsey. The most common contact allergens. Arch. Dermatol. 108:74-78, 1973.

Dorigan, J., B. Fuller, and R. Duffy. Scoring of Organic Air Pollutants. Chemistry, Production, and Toxicity of Selected Synthetic Organic Chemicals. MITRE Corp. 1976.*

Hawley, G. G. (ed.). The Condensed Chemical Dictionary, 8th ed. New York, Van Nostrand Reinhold Co. 1971.

Newsome, W. H., J. B. Shields, and D. C. Villeneuve. Residues of maneb, ethylenethiuram monosulfide, ethylenethiourea, and ethylenediamine on beans and tomatoes field treated with maneb. J. Agr. Food Chem. 23(4):756-758, 1975.

NIOSH. Registry of Toxic Effects of Chemical Substances. 1977.

North American Contact Dermatitis Group. The frequency of contact sensitivity in North America 1972-74. Contact Dermatitis 1:277-280, 1975.

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*This document was prepared for the U.S. Environmental Protection Agency by the MITRE Corp. It is a secondary source and does not cite its primary references. Thus, verification of some information is not possible. The environmental release data were taken from NSF/Rann Research Program on Hazard Priority Ranking of Manufacturing Chemicals.

Petrozzi, J. W., and R. N. Shore. Generalized exfoliative dermatitis from ethylenediamine. Arch. Dermatol. 112:525-526, 1976.

Provost, T. T., and O. P. Jillson. Ethylenediamine contact dermatitis. Arch. Dermatol. 96:231-234, 1967.

SRI (Stanford Research Institute). Directory of Chemical Producers. Menlo Park, Calif. 1978.

Van Hecke, E. Ethylenediamine sensitivity from exposure to epoxy resin hardeners and Mycolog cream. Contact Dermatitis 1:344-348, 1975.

Wiithrich, B. Occupational eczema due to ethylenediamine in the synthetic fiber manufacturing industry. Berufs-Dermatosen 20(4):200-203, 1972. (As stated in Biol. Abstr.)

# CHEMICAL HAZARD INFORMATION PROFILE

## Hexachlorocyclopentadiene

Date of report: March 15, 1977

This chemical was chosen for study because of its detection in air, water, and fish samples.

The following recommendations are made regarding further OTE evaluation of the possible health or environmental hazards of hexachlorocyclopentadiene (HCCPD):

(1) Check TSCA inventory for production volume--Reliable production information is not currently available.

(2) Wait for hazard assessment document from ORNL--Further OTS assessment at this point would simply be duplicative of ORNL's effort.

(3) Update this Chemical Hazard Information Profile based upon the additional information obtained.*

(4) Refer to Office of Solid Waste--HCCPD has been identified as a waste by-product of pesticide manufacture.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

## Chemical Identity

Hexachlorocyclopentadiene (HCCPD) is a dense, oily, slightly water-soluble liquid used commercially as an intermediate. Only two companies produce HCCPD in the United States: Hooker Chemical Co. at Montague, Mich., and Niagara Falls, N.Y., and Velsicol Chemical Corp. at Memphis, Tenn. (SRI, 1978). Hooker sells HCCPD as C-56 ; it is occasionally referred to in the literature as "hex."

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*Subsequent to the review of this CHIP document and the selection of the tentative dispositions given above, the TSCA Interagency Testing Committee recommended hexachlorocyclopentadiene for priority consideration under Section 4(a) of TSCA (44 F.R. 31866).

The important products derived from HCCPD (via Diels-Alder reactions) are the chlorinated cyclodiene insecticides aldrin, dieldrin, endrin, chlordane, heptachlor, endosulfan, Kepone®, and mirex; the fire-retardant monomers chlorendic acid (CA) and chlorendic anhydride (CAN), used primarily in polyester resins for marine, automotive, and construction applications, and to a lesser extent in alkyd resin coatings; and the fire-retardant plastic additives known as Dechloranes®. (In the past, Dechlorane® was the trade name under which mirex was sold for use as a fire-retardant additive.) The insecticide dienochlor is also derived from HCCPD, but via catalytic reduction rather than a Diels-Alder reaction. The chemical structures of HCCPD and these derivatives are shown in the appendix.

## Production and Use

Because there are but two producers of HCCPD, production statistics are not public information. Lu et al. (1975) stated that production of HCCPD could not be less than 50 million lb per year, based on production levels of the chlorinated insecticides for the early 1970's. This estimate, however, preceded EPA actions taken against most of these insecticides, which have severely limited their allowable applications. Within the past 2 years aldrin and dieldrin have had their registrations canceled, chlordane and heptachlor have had their registrations suspended, and endrin and Kepone® have been presumed against. Limited, specific uses of aldrin/dieldrin and chlordane/heptachlor are permitted under their respective cancellation and suspension orders. The current mirex formulation is to be phased out by 1978 and replaced by a new formulation. Dienochlor and endosulfan have not had any action taken against them to date.

The chlorendic acid/chlorendic anhydride outlet for HCCPD is a significant market. An estimated 10 million lb of CA/CAN was produced in 1974, and the expected growth rate is 10%/year through 1980 (SRI, 1976). Production of 10 million lb of CA/CAN requires 7-7.5 million lb of HCCPD. These compounds are also produced only by Hooker and Velsicol.

The production levels of the Dechlorane® fire retardants are unknown. Dechlorane fire retardants are Hooker products.

Based on the above, HCCPD production at this time is at least 7 million lb per year and is substantially less than 50 million lb per year. Using data on current production capacities of dienochlor and endosulfan, allowing for some small production of the canceled and suspended insecticides for their few allowable uses, and assuming that Dechlorane® fire-retardant production is on the order of 1 million lb per year, an upper limit on current HCCPD production of 15 million lb per year can be assumed.

## Health Aspects

The toxicological hazards (particularly carcinogenicity), persistence, and widespread environmental contamination with certain of the HCCPD-derived insecticides are well known (IARC, 1974), and these features have formed the basis of the restrictive actions that have been taken against them. Very little is known about the health and environmental effects of HCCPD, and the available information on CA/CAN and the Dechlorane® materials is practically nonexistent.

HCCPD produces systemic toxicity of unknown mechanism in mammals via ingestion, inhalation, and dermal exposure. Degenerative changes in the brain, heart, adrenals, liver, kidneys, and lungs are observed in severely poisoned animals by all routes of administration. The oral $LD_{50}$ in rats is 500-600 mg/kg. Rats receiving 30, 100, or 300 ppm HCCPD in their diets did not show any abnormalities after 90 days. Rats fed 0.002, 0.0002, or 0.00002 mg/kg daily for 6 months showed no abnormalities. The minimum lethal dose of HCCPD applied to rabbit skin is 430-610 mg/kg. Rats, rabbits, and guinea pigs survived 150 7-hr exposures to 0.15 ppm HCCPD in the air over a 216-day period; however, this exposure level was lethal to four of five mice. All species showed mild degenerative changes in the liver and kidneys. Most animals in all four of these species died from a single 7-hr exposure to 3.2 ppm HCCPD in the air (Ingle, 1953; Treon et al., 1955; Naishstein and Lisovskaya, 1965).

No data are available on the carcinogenicity, mutagenicity, or teratogenicity of HCCPD.

For aquatic species, the reported 96-hr TLM's are 25 ppm for sunfish, 20 ppm for bass, and 0.059 ppm for fathead minnows (Davis and Hardcastle, 1959; U.S. DHEW, 1956).

A model ecosystem study showed that HCCPD has considerable ecological stability and moderate biomagnification potential in aquatic organisms (Lu et al., 1975).

HCCPD has been qualitatively identified as a contaminant in the discharge of a pesticide production plant (probably Velsicol) in Memphis, Tenn., on seven occasions, most recently in December 1975 (Donaldson, 1977). This past May at the Hooker plant in Michigan, HCCPD was qualitatively identified in air, in the plant's aqueous discharge (56 ppb; 170 ppb), and in fish tissue in the receiving stream (4-18 ppb). According to Dennis Swanson of the Michigan State Department of Natural Resources, Hooker has agreed to limit the HCCPD in its aqueous discharge to 10 ppt (limit of detection).

The only effects information available for CA/CAN is an LD50 value of 0.5 g/kg for CAN given to rats via stomach tube (Kowalski and Bassendowska, 1965). No reports of environmental contamination with CA/CAN were found.

## Environmental Aspects

No information was found in the sources consulted on the environmental fate or effects of HCCPD.

## REFERENCES

Davis, J. T., and W. S. Hardcastle. Biological assay of herbicides for fish toxicity. Weeds 7:397-404, 1959.

Donaldson, W. Analytical Chemistry Branch, Environmental Research Laboratory, Athens, Ga., private communication, 1977.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man: Some Organochlorine Pesticides (vol. 5). 1974.

Ingle, L. Toxicity of chlordane vapors. Science 118: 213-214, 1953.

Kowalski, Z., and E. Bassendowska. Acute toxicity of phthalates used in the plastic industry. Med. Pr. 16(2):109-112, 1965.

Lu, P., R. L. Metcalf, A. S. Hirive, and J. W. Williams. Evaluation of environmental distribution and fate of hexachlorocyclopentadiene, chlordene, heptachlor, and heptachlorepoxide in a laboratory model ecosystem. J. Agr. Food Chem. 23(5):967-973, 1975.

Naishstein, S. Ya., and E. V. Lisovskaya. Maximum permissible concentration of hexachlorocyclopentadiene in water bodies. Gig. Sanit. 30:117-181, 1965.

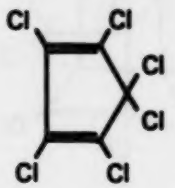
SRI (Stanford Research Institute). Chemical Economics Handbook (Unsaturated Polyester Resins; Maleic Anhydride). Menlo Park, Calif. 1976.

SRI. Directory of Chemical Producers, United States of America. Menlo Park, Calif. 1978.

Treon, C., F. Cleveland, and J. Cappel. The toxicity of hexachlorocyclopentadiene. Arch. Ind. Health 11:459-472, 1955.

U.S. Department of Health, Education, and Welfare (DHEW). Bio-Assay Investigations for International Joint Commission. Hooker Electrochemical Co., Niagara Falls, N.Y. 1956.

## APPENDIX. Chemical Structures



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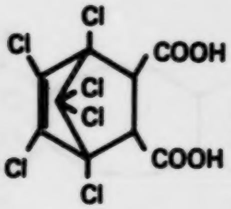

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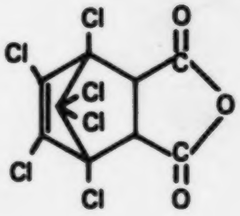

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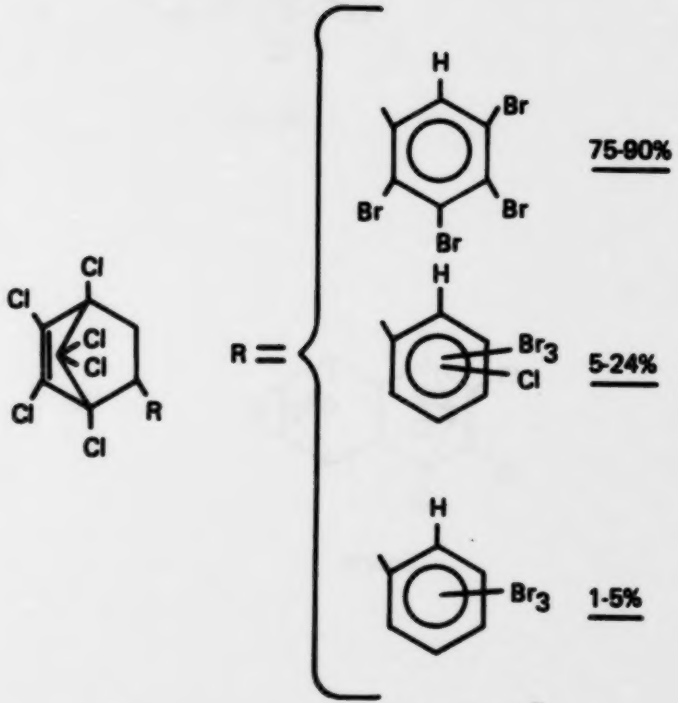

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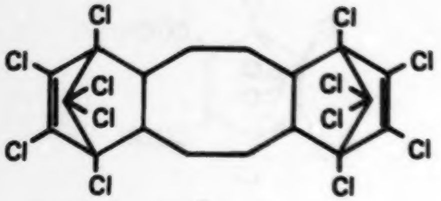
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Dechlorane 25®
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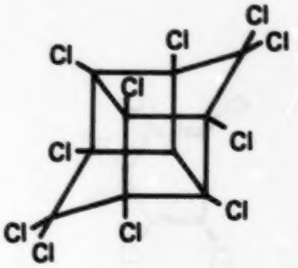
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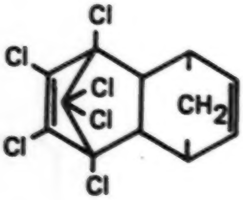
Mirex (was formerly Dechlorane® as well)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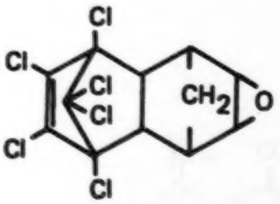
Aldrin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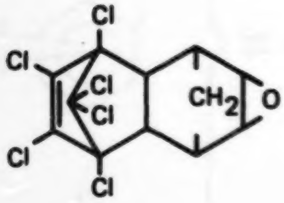
Dieldrin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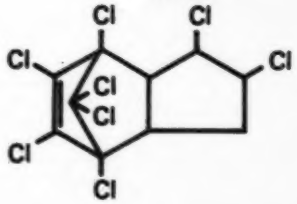
Endrin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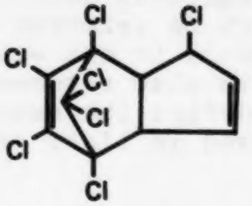
Chlordane

# APPENDIX (Continued)



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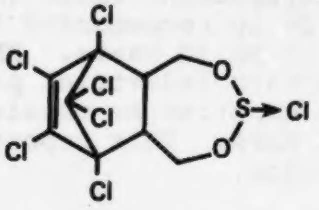
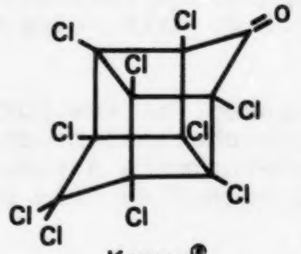
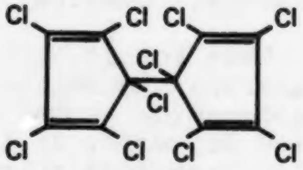


**Endosulfan**



**Kepone®**



**Dienochlor**

# CHEMICAL HAZARD INFORMATION PROFILE

## Hexamethylphosphoramide

Date of report: August 1976

This chemical was chosen for study because of a report that hexamethylphosphoramide (HMPA) induced squamous cell carcinoma in rats. It is recommended that this report be referred to the Office of Solid Waste. HMPA has been found in the waste products from certain industrial processes. It is also recommended that 8(a) information be obtained to better define the exposure potential of HMPA. This report will be revised in light of the 8(a) information.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

This report with attachments was prepared for the purpose of organizing the available information on the chemical hexamethylphosphoramide (HMPA) and to review the developments during the period September 1975 through August 1976 regarding this potentially hazardous substance.

On September 24, 1975, Dr. C. F. Reinhardt of E. I. du Pont's Haskell Laboratory notified NIOSH that HMPA induced squamous cell carcinoma of the nasal cavity in rats inhaling 400 to 4,000 ppb (by volume) of the material for 6 hr per day, 5 days per week for 8 months (Attachment I). Although no cancerous lesions were observed in rats exposed to 50 ppb at the end of 8 months, a subsequent report noted the same effect at this level beginning after 13 months of exposure (Attachment II). The Office of Toxic Substances was notified of this finding on October 1, 1975, and undertook a quick survey of the available information on HMPA to determine its current uses, potential for environmental release, and other toxicological features. A brief memo dated October 10, 1975, was prepared by the Early Warning Branch (Attachment III). A more detailed report was prepared by NIOSH, dated October 24, 1975, which concentrated on potential occupational exposure to HMPA (Attachment IV).

The significant information developed in these initial studies is the following. HMPA is known to be produced in the United States by du Pont at Deepwater, N.J.; Chemical Samples Co. at Cleveland, Ohio; and Fike Chemical Co. at Nitro, W. Va. Du Pont does not sell HMPA, but ships it to their Spruance, Va., plant for use in the production of its Kevlar® polyaramid product. The other two companies sell HMPA, and both domestic and some imported HMPA is distributed by about 11 other companies. The quantity of HMPA produced and sold annually is unknown.

HMPA is used as a solvent in research laboratories and, according to the NIOSH report, this constitutes the major source of occupational exposure. HMPA has been studied for its activity as an insect chemosterilant, but it is not used commercially as such. HMPA has also been studied for use in PVC resins as a UV light inhibitor, as a jet fuel deicing agent, as a flame retardant, and as an antistatic agent (Merck Index, 1968). The only known commercial use of HMPA appears to be as a speciality solvent by du Pont for the manufacture of the Kevlar® product as mentioned above. According to du Pont, the finished Kevlar® product contains less than 1 ppm HMPA by weight which is bound firmly to the fiber. It is du Pont's belief that this does not pose a hazard to persons handling the finished Kevlar® fiber (Attachment I).

Very little additional data on the biological effects of HMPA was found. $LD_{50}$ values range from 2,500-3,500 mg/kg in rats exposed orally, cutaneously, or intradermally; 2,600 mg/kg in rabbits exposed cutaneously; and 835 mg/kg in chickens exposed orally (NIOSH, 1975). Acute systemic toxicity includes alterations in the renal, gastrointestinal, and nervous systems (Kimbrough and Gaines, 1966; Kimbrough and Sedlack, 1968; Shott et al., 1971). Inhaled HMPA enhances chronic murine pneumonia in rats (Overcash, 1973). HMPA is a mutagen for fruit flies (Benes and Sram, 1969). Studies on human (Chang and Klassen, 1968) and mouse (Manna and Das, 1973) chromosomes revealed no increased frequency of HMPA-induced chromosomal aberrations compared to controls. Testicular atrophy and aspermia have been noted in rats receiving HMPA orally (Jackson et al., 1970). HMPA also inhibits testicular development in orally dosed cockerels (Sherman and Herrick, 1970).

NIOSH estimated that 5,000 persons are occupationally exposed to HMPA, of which more than 90% involve exposure in research laboratories (Attachment IV). Except for the possible exposure through residual HMPA in Kevlar®, no nonoccupational human exposure was identified.

No data were available in 1975 on levels of HMPA in environmental samples, nor on the persistence, bioaccumulation potential, or other possible effects of HMPA as an environmental contaminant.

Because of the limited production and the use pattern of HMPA, widespread environmental contamination did not appear likely, and the focus of concern remained on occupational exposures.

In April 1976, du Pont supplied data to EPA Region III regarding levels of HMPA in the liquid discharge of the Spruance, Va., plant into the James River during January-March 1976 and the levels of HMPA in the atmosphere within and around this same plant (Attachment V). These data indicated that 48 lb of HMPA was being discharged daily into the James River during January, 63 lb per day during February, and 22 lb per day during March. Measurements in the James River below the plant discharge site showed levels of HMPA at about 0.5 ppb, the lower limit of detectability. Some limited data were also supplied on the acute effects of HMPA to aquatic life. Using 96-hr static, unaerated conditions, the $LC_{50}$ of HMPA was found to be 7,500 ppm for bluegill sunfish and 6,495 ppm for Daphnia magna. Outside air concentrations of HMPA were below 0.05 ppb (limit of detection) in samples taken within the confines of the plant and in off-plant locations (0.5 to 1 mile distant). Air concentrations within the operating areas of the plant were below 0.5 ppb, except for small regulated areas where concentrations up to 50 ppb were observed. Personnel in these latter areas are required to use respirators.

In the same report, du Pont described improvements in control equipment and procedures at the Spruance plant to reduce HMPA losses to the environment in air, in water, and through solid waste disposal. These improvements include elimination or control of HMPA leaks in process equipment, relocation of primary exhaust to a high-elevation stack, incorporation of activated carbon to remove HMPA from liquid waste streams, and incineration of Kevlar® process solid wastes on-site and through a disposal contractor. Prior to this, the solid wastes were apparently not incinerated, but were stored in drums on a private land disposal site near Anniston, Ala.

In early 1976, there was some concern that the storage of Kevlar® solid wastes at the Anniston site might result in HMPA contamination of local drinking water (Attachment VI). EPA Region IV, together with du Pont, investigated the site where about 5,000 steel and cardboard drums representing several years worth of Kevlar® process waste were being stored. The material in the drums consisted of about 80% sulfuric acid and 20% inert polymers, with about 20-30 ppm HMPA present initially. The HMPA supposedly would break down in the sulfuric acid to phosphoric acid and phosphate salts. Some of the containers had corroded, and because of the presence of a well on the disposal site and general runoff considerations, contamination of water systems could have occurred. Detectable levels of HMPA were found in the water and sediment of a drainage ditch downstream from the disposal site, in the well at the disposal site, and in a private well upgrade from the disposal site. No HMPA was detected in the raw or finished drinking water of Anniston. Du Pont agreed to remove the drums from the site and have the contents incinerated; EPA planned to lime the disposal site and seal the on-site well.

Overall, the HMPA problem appears to be receiving adequate attention both by industry and the concerned Government agencies. As indicated by the information developed initially, the major focus of concern over HMPA remains with occupationally exposed individuals, and no intensive study of HMPA as a critical environmental problem by the Office of Toxic Substances is warranted. The Office of Toxic Substances will retain an up-to-date file on HMPA to facilitate rapid response to any future developments. As suggested in the October 10, 1975, Early Warning Branch memo (Attachment III), information on the production and uses of compounds chemically related to HMPA has been developed. This package (Attachment VII) is now under review by the Early Warning Branch.

## REFERENCES

Benes, V., and R. J. Sram. Mutagenic activity of some pesticides in Drosphila melanogaster. Ind. Med. Surg. 38(12):442-444, 1969.

Chang, T. H., and W. Klassen. Comparative effects of tretamine, tepa, apholate, and their structural analogs on human chromosomes in vitro. Chromasoma 24(3):314-323, 1968.

Jackson, H., A. R. Jones, and E. R. A. Cooper. Effects of hexamethylphosphoramide on rat spermatogenesis and fertility. J. Reprod. Fert. 20:263-269, 1970.

Kimbrough, R. D., and J. B. Gaines. Toxicity of hexamethylphosphoramide in rats. Nature 211:146-147, 1966.

Kimbrough, R. D., and V. A. Sedlack. Lung morphology in rats treated with hexamethylphosphoramide. Toxicol. Appl. Pharmacol. 12(1):60-67, 1968.

Manna, G. K., and P. K. Das. Effect of two chemosterilants, apholate and hempa, on the bone-marrow chromosomes of mice. Can. J. Genet. Cytol. 15(3):451-459, 1973.

The Merck Index, 8th ed. Rahway, N.J., Merck and Co. 1968. p. 528.

NIOSH. Registry of Toxic Effects of Chemical Substances. 1975. p. 903.

Overcash, R. G. Enhancement of natural and experimental chronic respiratory disease in the rat by oral hexamethylphosphoramide. Z. Rechtsmed. 1973.

Sherman, M., and R. B. Herrick. Acute toxicity of five insect chemosterilants, hemel, hempa, tepa, metepa, and methotrexate, for cockerels. Toxicol. Appl. Pharmacol. 16:100-107, 1970.

Shott, L. D., A. B. Borkovek, and W. A. Knapp. Toxicology of hexamethylphosphoric triamide in rats and rabbits. Toxicol. Appl. Pharmacol. 18(13):499-506, 1971.

## ATTACHMENTS*

I. Letter from Dr. C. F. Reinhardt, Haskell Laboratory for Toxicology and Medicine, E. I. du Pont and Co., to Dr. John Finklea, Director, NIOSH, September 24, 1975.

II. Two-Year Inhalation Toxicity Study on Hexamethylphosphoramide (HMPA): One Year Interim Report, H. J. Trochimowicz, J. W. Sarver, K. P. Lee, and S. P. Shrivastava (Haskell Laboratory for Toxicology and Medicine, E. I. du Pont and Co.), presented at the American Industrial Hygiene Association Meeting, May 19, 1976, Atlanta, Ga.

III. "Hexamethyl phosphoramide (HMPA)," memo from Frank Letkiewicz to Dr. Farley Fisher, Chief, Early Warning Branch, OTS, October 10, 1975.

IV. Background Information on Hexamethylphosphoric Triamide, Office of Occupational Surveillance and Biometrics, NIOSH, October 24, 1975.

V. Letters from Mr. Howard Kress, plant manager, Spruance plant, du Pont, to Mr. Ralph Rhodes, Toxic Substance Coordinator, EPA Region III, April 14, 1976; April 30, 1976.

VI. (a) "Disposal of Hazardous Waste In and Near Anniston, Alabama," memo from Elmer Cleveland, EPA Region IV, to the Record, May 17, 1976.

(b) "Investigation of Possible Environmental Damage from 'Kevlar' Waste Products Stored Near Anniston, Alabama," memo from William Davis, EPA Region IV, to James Fringer, Director, Surveillance and Analysis Division, EPA Region IV, May 17, 1976.

(c) Letter from M. D. Lair, Chief, Engineering Section, Water Surveillance Branch, EPA Region IV, to Mr. Robert Spenser, E. I. du Pont de Nemours and Co., Inc., June 4, 1976.

VII. Compilation of Information on Chemicals Structurally Related to HMPA, prepared by Tracor-Jitco, Inc., under contract 68-01-3255, Task #8.

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*Attachments I-VII are available in the OPTS public reading room located in Room E447 at EPA Headquarters.

# CHEMICAL HAZARD INFORMATION PROFILE

## n-Hexane

Date of report: May 13, 1977

This chemical was chosen for study because of its reported involvement in occupational polyneuropathies.

The following recommendations are made regarding further OTE evaluation of the possible health or environmental hazards of n-hexane:

(1) Defer to the actions of NIOSH and OSHA--Possible occupational problems will be addressed in a NIOSH Criteria Document.

(2) Transmit this report to OAQPS--Atmospheric losses of n-hexane may cause significant local exposures.

(3) Transmit this report to CPSC--n-Hexane may be used as a solvent in consumer products such as glues and cleaning fluids.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

### Chemical Identity

n-Hexane is a saturated straight-chain hydrocarbon with the molecular formula $C_6H_{14}$. At room temperature n-hexane is a colorless, very volatile liquid (boiling point, 69°C) with a faint, peculiar odor. n-Hexane is insoluble in water but fairly soluble in organic solvents (alcohol, ether, and chloroform) (Merck Index, 1976).

### Production and Use

The three most commonly used charge stocks for the production of commercial hexanes are straight-run gasoline, the higher boiling portion of the liquid product stripped from natural gas, and a refinery stream known as "BTX raffinate" (the paraffinic portion that remains after the removal of benzene, toluene, and xylene from a naphtha which has been refined to convert naphthalenes to aromatics). Two basic methods are used in the manufacture of n-hexane from these three stocks. One involves the close fractionation of feedstocks which separates n-hexane on the basis of boiling point. The second, more recently developed method of production uses adsorption on "molecular sieves" to separate the hexane product from the crude stocks. A molecular sieve is an adsorbent material of closely controlled pore size which allows normal paraffins to pass into the pores and be adsorbed while rejecting branched-chain paraffins, naphthenes, and aromatics. Molecular sieve separation permits the manufacturer to produce a hexane product of almost any desired n-hexane composition through adjustments in the operating cycle. The composition of fractionated hexanes, on the other hand, depends on the constitution of the charge stocks and thus offers the producer much less leeway in final product selection (Porter, 1964).

The compositions of three typical commercial hexanes are listed in Table 1. These examples illustrate the wide range of hydrocarbon distribution and minor impurity content that may be encountered in commercial products. Hexanes of many different combinations of components are the norm for the market (Porter, 1964).

Annual production of n-hexane is estimated at four billion pounds (EPA, 1979).

The chief commercial uses of hexane are as a solvent for the extraction of oil seeds, a reaction medium, and a component in the formulation of various products. Extraction of oil seeds is the single largest volume use of hexane. Hexane is the solvent of choice for this purpose because of its high solvency for seed oil, the low boiling point of the solvent, giving easy separation of hexane from the oil and meal, and also hexane's low toxicity and cost. A narrow boiling hexane is required to hold down solvent losses during separation, and low benzene content is necessary to minimize toxicity (Porter, 1964).

Hexane is used in the extraction of the following oil seeds: soybeans, cottonseed, flaxseed, safflower seed, corn germ, peanuts, and several other smaller volume seeds. Soybeans and cottonseed represent the greatest extraction volume based on hexane (Porter, 1964).

Hexane is used extensively as a reaction medium in the production of polyolefins, certain elastomers, and pharmaceuticals. Examples of the first two categories are polypropylene, polyisopropene, high-density polyethylene, and ethylene-propylene rubber. The solvent serves as a catalyst carrier and at times acts to control final product molecular weight by dropping the polymer out of solution when a certain molecular size is attained. Hexane for this use must be relatively pure or the reaction may be adversely affected (Porter, 1964).

Table 1. Composition of Typical Commercial Hexanes (volume %)

| | Hexane A[a] | Hexane B[b] | Hexane C[c] |
|---|---|---|---|
| n-Hexane | 44.4 | 86.5 | 60.9 |
| 2,3-Dimethylbutane | 1.7 | trace | 0.3 |
| 2-Methylpentane | 17.2 | 0.3 | 9.3 |
| 3-Methylpentane | 18.6 | 4.5 | 22.7 |
| Methylcyclopentane | 16.2 | 8.7 | 6.7 |
| Cyclohexane | 1.8 | -- | 0.1 |
| Benzene | 0.06 | 0.01 | -- |
| Boiling range, °C | 65.5-70.0 | 68.1-68.6 | 66.0-68.2 |

Source: Adapted from Porter, 1964.

[a] This product was fractionated from straight-run gasoline. Note that it is relatively low in n-hexane, relatively high in olefins, has a wide boiling range, and contains a number of minor impurities.

[b] This hexane is the result of the extremely close fractionation (as evidenced by the narrow boiling range) of a natural gas liquid stock. This relatively pure commercial hexane has a high concentration of n-hexane and relatively small amounts of various impurities.

[c] A BTX raffinate stock was fractionated to produce this hexane. The low concentration of benzene is characteristic of a BTX raffinate stock. This hexane is intermediate in purity between the two preceding examples.

The third major use of hexane is as a product component. Hexane is found in quick-drying cements, certain two-solvent-system adhesives (controls viscosity and reduces drying time), and some lacquers and printing inks where a quick drying diluent is desired (Porter, 1964).

## Health Aspects

The acute toxicity of n-hexane is primarily that of a local irritant and, in larger doses, a CNS depressant with symptoms such as dizziness, numbness in extremities, and difficulty in walking (ITII, 1976; Herskowitz et al., 1971). Chronic exposure to n-hexane concentrations of approximately 500 ppm for several months can lead to progressive peripheral nervous system involvements in a dose-related manner. Polyneuropathy begins insidiously 2-6 months (or longer, depending on the individual and the level of exposure) after exposure to n-hexane commences, and continues for 2-3 months after exposure has ceased. The polyneuropathy can be either sensory of the "glove and stocking" type or sensorimotor with or without muscle atrophy. Slight optic nerve involvement may occur, but there are no indications of CNS lesions (Shirabe et al., 1974). Severe cases may exhibit peripheral nervous system demyelination and axonal degeneration, denervation of muscles, and slow clinical recovery. Recovery, however, does occur and is generally complete except in very severe instances where permanent neurological damage can result (Herskowitz et al., 1971).

### Human

There are many documented cases of deleterious effects from n-hexane exposure in industrial situations.

Three New York cabinet finishers were exposed by oral, inhalation, and dermal means to an open vat of an n-hexane-containing solvent. Average n-hexane levels in the air were 650 ppm, with peaks at 1,300 ppm. The workers all developed polyneuropathy after a few months exposure but recovered completely when n-hexane exposure ceased (Herskowitz et al., 1971).

Paulson and Waylonis (1976) reported a study concerning a printing plant where at least 8 of 50 total workers exposed to n-hexane developed a mild and recurrent neuropathy with no CNS involvement. The plant produced a printed paper product with an adhesive backing; n-hexane was released by the drying adhesive. n-Hexane levels peaked at 4,060 mg/m$^3$ (1,150 ppm) in portions of the plant. The study covered 25 years.

Abbritti et al. (1976) postulated that nearly 400 cases of polyneuropathy between 1957 and 1973 formerly attributed to TOCP, as well as 122 newly documented cases of polyneuropathy in the

Italian shoe industry, were actually due to $C_5$ and $C_6$ alkane exposure. Chemical analysis of glues and cleaning fluids used in several factories with incidents of polyneuropathy showed the presence of low-boiling paraffinic hydrocarbons (n-hexane, pentane, 2-methylpentane, 3-methylpentane, etc.) in concentrations of over 80% by weight.

Two leather factory workers developed polyneuropathy following exposure to an n-hexane-containing glue. Tests on the factory air showed a total "solvent" level greater than 500 ppm. n-Hexane was not positively identified as the causative agent, but likely contributed to the difficulty (Assouly et al., 1972).

Four cases of polyneuropathy in Japan were linked to an n-hexane containing solvent used in a printing process (Yoshida et al., 1974).

Yamamura (1969) reported 93 cases of polyneuropathy in the Japanese sandal industry. A rubber adhesive was the source of the n-hexane, and air concentrations between 500 and 2,500 ppm were found. There were several severe cases, with some individuals displaying cranial neuropathy and permanent damage.

There are many documented cases of n-hexane induced polyneuropathy following deliberate chronic glue sniffing (Altenkirch and Mager, 1976; Shirabe et al., 1974; Asbury et al., 1974).

## Laboratory Animals

Several experiments dealing with the effects of n-hexane on lab animals were located and have been summarized.

Kimura et al. (1971) reported the (acute) oral $LD_{50}$ values for undiluted n-hexane in rats of various ages. n-Hexane was significantly more toxic in the youngest group (14 days old), producing an oral $LD_{50}$ (ml/kg) of 24.0 as compared with the two older groups producing an $LD_{50}$ of 49.0 in the young adults and an $LD_{50}$ of 43.5 in the older adults (Kimura et al., 1971).

Bohlen et al. (1973) explored the kinetics of uptake and distribution of n-hexane in rat tissue following exposure to an atmosphere containing approximately 5% n-hexane. The blood, brain, adrenals, kidneys, and spleen attained a saturation value within 4-5 hr. The liver n-hexane concentration, however, increased linearly with exposure and did not reach saturation within 10 hr. This observation was explained on the basis of an n-hexane induced accumulation of triglycerides in the liver. A correlation was established between the value of the hexane saturation point and the total lipid content of each organ.

Truhaut et al. (1973) found that rats exposed for 5-6 months to an atmosphere containing 2,000 ppm hexane developed various neurological difficulties. Electrophysical measurements showed decreased conduction velocity, increased refractory period, and decreased excitability. Histological examination revealed demyelination.

Bonashevskaya and Partsef (1971) explored the effects on rats of "expected" urban atmospheric levels of mixtures of equal parts of n-hexane and pentane ranging from 3.0-94.7 mg/m$^3$ (0.8-26.3 ppm). The rats receiving the higher concentrations were significantly affected in a dose-related manner. Observed damage included structural changes in the cerebral cortex, alterations in the motor chronaxy of muscle antagonists (less excitable), and injury to apical dendrites of neurons. The lowest exposure group (3.0 mg/m$^3$) was unaffected. All groups were exposed for 2 months.

Kramer et al. (1974) demonstrated that n-hexane is rapidly hydroxylated in mice by the liver. DiVincenzo et al. (1976) identified these metabolites as 5-hydroxy-2-hexanone and 2,5-hexanedione in guinea pigs. These n-hexane metabolites were identical to those found following methyl-n-butyl ketone (MnBK) exposure in guinea pigs, which suggests that a common metabolic pathway may exist for the neuropathy. MnBK was implicated in several cases of peripheral neuropathy affecting factory workers in a plastic coating-printing plant. The neurological pattern was that of a distal, motor, and sensory disorder with minimal reflex loss. The onset of the condition was invariably insidious. The authors noted the similarity between the effects of hexane and MnBK and attributed this to the possible biotransformation of each to the same active metabolite (Abdel-Rahman et al., 1976). 2,5-Hexanedione, when administered as such to rats, produced varying degrees of peripheral neuropathy in that species also (Raleigh et al., 1975; Spencer and Schaumburg, 1975).

Foa et al. (1976) showed that n-hexane alone had no neurological effect on pigeons when administered by inhalation or percutaneous means (8% pure n-hexane in an inhalation chamber for 5 hr/day, 5 days/week for 17 weeks; a second group received approximately the same dose for the same period of time by percutaneous means). No clinically discernible alterations of the nervous system were noted at the experiment's conclusion. Subsequent neurophysiological and histopathological examinations also revealed no noticeable alterations of the nervous system. The conclusion reached was that n-hexane can only induce neurological change when in combination with other solvents (if n-hexane is involved at all). These results have not been corroborated.

Hexane lethality in rats is modified by changes in environmental temperature. An increase from 26° to 36°C decreased the lethal dose from 9,100 to 530 mg/kg. Conversely, temperature depression increased the lethal dose to 4,000 mg/kg at 8°C (Keplinger et al., 1959).

## Environmental Aspects

The following are brief descriptions of the most pertinent environmental concerns associated with n-hexane.

### Oil Seed Extraction Losses

The loss of n-hexane from oil seed extraction facilities may represent a serious local problem. Porter (1964) estimated that atmospheric losses of n-hexane in "modern" soybean extraction plants generally run between 0.5 and 1.0 gallon of n-hexane per ton of soybeans extracted; losses at older plants are expected to be greater. Using Porter's (1964) figures, the daily loss will be 600 gallons or 2.2 ($10^5$) gallons annually.

The n-hexane emissions from other types of oil seed extraction facilities are not known, although Porter (1964) reports that solvent losses from cottonseed and flaxseed extraction sites generally exceed those encountered at soybean plants.

Localized release of these large amounts of n-hexane may represent a very real health hazard, especially in terms of chronic exposure (for which there are no available toxicity data).

### Mobile Source Emissions

Hydrocarbons emitted from all mobile sources were estimated to equal 13.8 million tons per year in 1970. n-Hexane was estimated to represent 1.2 volume percent of total emitted hydrocarbons (equivalent to roughly 0.17 million tons of hexane). This percentage was expected to decrease after 1972 because of the mandatory use of catalytic converters on some passenger cars (CIIT, 1977).

### Losses from the Synthetic Elastomer Industry

n-Hexane is one of many solvents (others include pentane, heptane, benzene, cyclohexane, chlorobenzene, etc.) used in the synthetic elastomer industry as the reaction medium in both the solution and emulsion procedures. The magnitude of the solvent losses expected from this industry is difficult to assess. There are a number of opportunities for solvent escape: during production of the elastomer; while stripping the solvent from the finished product; and various fugitive losses occurring during the storage and pumping of the solvent.

Given the great production volume of the synthetic elastomer industry, the potential for environmental abuse arising from solvent release may be an appreciable problem in the locale of the plant sites. The loss of solvents other than n-hexane may prove more of a problem given the greater demonstrated toxicity of several of the listed solvents. The scope of the problem, however, remains ill defined owing to the paucity of available information.

## Other Considerations

n-Hexane, like other vapor-phase organic pollutants of hydrocarbon origin, produces no pronounced effect on the physical properties of the atmosphere, does not decrease visibility or affect the amount of solar radiation, and does not alter precipitation patterns. The possibility that n-hexane, as a relatively nonreactive paraffin, enters into the photochemical reaction leading to the formation of peroxyacetylnitrate (PAN) has not been reported. However, hydrocarbons similar to n-hexane (n-pentane and methyl pentane) have been implicated in PAN formation (NAS, 1976).

NOTE: 500 ppm n-hexane equals approximately 1,800 $mg/m^3$ (ACGIH, 1971).

## REFERENCES

Abbritti, G. et al. Shoe-makers' polyneuropathy in Italy: The aetiological problem. Br. J. Ind. Med. 33:92-99, 1976.

Abdel-Rahman, M. S. et al. Toxicity and metabolism of methyl n-butyl ketone. Am. Ind. Hyg. Assoc. J. 37(2):95, 1976.

ACGIH (American Conference of Governmental Industrial Hygienists). Documentation of the Threshold Limit Values for Substances in Workroom Air. 1971.

Altenkirch, H., and J. Mager. Toxic polyneuropathy after sniffing contact glue thinner. Dtsch. Med. Wochenschr. 101:195-198, 1976. (Abstract)

Asbury, A. K. et al. Glue sniffing neuropathy. J. Neuropathol. Exp. Neurol. 33(1):99, 1974.

Assouly, M. et al. Polyneuritis caused by n-hexane. Arch. Mal. Prof. Med. Trav. Secur. Soc. 33(6):309-310, 1972. (Abstract)

Bohlen, Peter et al. Uptake and distribution of hexane in rat tissues. Toxicol. Appl. Pharmacol. 25:242-249, 1973.

Bonashevskaya, T. I., and D. P. Partsef. Experimental studies of the effects of microconcentrations of a mixture of pentane and hexane in air. Hyg. Sanit. 36:339-343, 1971. (Engl. trans.)

CIIT (Chemical Industry Institute of Toxicology). CIIT Current Status Reports, No. 1, n-Hexane. 1977.

Directory of Chemical Producers - U.S.A. Menlo Park, Calif., Stanford Research Institute. 1978.

DiVincenzo, G. D. et al. Characterization of the metabolites of methyl n-butyl ketone, methyl iso-butyl ketone, and methyl ethyl ketone in guinea pig serum and their clearance. Toxicol. Appl. Pharmacol. 36: 511-522, 1976.

Foa, V. et al. Experimental n-hexane neurotoxicity. Med. Lav. 67(2):136-144, 1976. (Summary)

Herskowitz, Allan, N. Ishii, and Herbert Schaumburg. n-Hexane neuropathy: A syndrome occurring as a result of industrial exposure. N. Engl. J. Med. 285(2):82-85, 1971.

ITII (International Technical Information Institute). Toxic and Hazardous Industrial Chemicals Safety Manual. Tokyo. 1976.

Keplinger, M. L. et al. Effects of environmental temperaure on the acute toxicity of a number of compounds in rats. Toxicol. Appl. Pharmacol. 1:156-161, 1959. (As cited in CIIT)

Kimura, Eugene T. et al. Acute toxicity and limits of solvent residue for sixteen organic solvents. Toxicol. Appl. Pharmacol. 19:699-704, 1971.

Kramer, A. et al. Effect of n-hexane inhalation on the monooxygenase system in mice liver microsomes. Chem-Biol. Interact. 8:11-18, 1974.

Lonneman, W. A. et al. Hydrocarbon composition of urban air pollution. Environ. Sci. Technol. 8(3):229-236, 1974.

The Merck Index, 9th ed. Rahway, N.J., Merck and Co., Inc. 1976.

NAS (National Academy of Sciences). Vapor-Phase Organic Pollutants, Committee on Medical Biologic Effects of Environmental Pollutants. 1976. (As cited in CIIT)

Paulson, George W., and George W. Waylonis. Polyneuropathy due to n-hexane. Arch. Intern. Med. 136:880-882, 1976.

Porter, C. A. Hexanes. In Kirk-Othmer Encyclopedia of Chemical Technology, 2nd ed., vol. 11. 1964.

Raleigh, R. et al. Methyl n-butyl ketone. Arch. Environ. Health 30:317-318, 1975. (As cited in CIIT)

Shirabe, Teruo et al. Toxic polyneuropathy due to glue sniffing. J. Neurol. Sci. 21:101-113, 1974.

Spencer, P. S. and H. H. Schaumburg. Experimental neuropathy produced by 2,5-hexadione - A major metabolite of neurotoxic industrial solvent methyl n-butyl ketone. J. Neurol. Neurosurg. Psychiatry 38(8):771-775, 1975. (As cited in CIIT)

Truhaut, R. et al. First electrophysiological results after experimental intoxication with technical hexane and heptane in the albino rat. Arch. Mal. Prof. 34(7-8):417-426, 1973. (Summary)

U.S. EPA. Toxic Substances Control Act Chemical Substance Inventory, Office of Pesticides and Toxic Substances, Washington, D.C. 1979.

U.S. Tariff Commission. Crude Products from Petroleum and Natural Gas. 1972-75.

Yamamura, U. n-Hexane polyneuropathy. Folia Psychiatr. Neurol. Jpn. 23:45-57, 1969. (As cited in Paulson and Waylonis and in Herskowitz et al.)

Yoshida, T. et al. Four cases of n-hexane polyneuropathy and its electrophysical studies. Clin. Neurol. 14:454-461, 1974. (Abstract)

# CHEMICAL HAZARD INFORMATION PROFILE

Isopropyl Alcohol
Date of report: December 29, 1977
Revised       : November 20, 1979

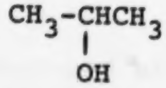
This chemical was chosen for study because of reported liver damage to workers in an isopropyl alcohol packaging plant. It was subsequently learned that the liver damage was actually due to isopropyl alcohol's potentiation of carbon tetrachloride hepatotoxicity.

It is recommended that isopropyl alcohol receive low priority for further assessment.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should be construed as final Agency policy with respect to the subject chemical.

## Chemical Identity



$$CH_3\text{-}\underset{\underset{OH}{|}}{C}HCH_3$$

Cas No.: 67-63-0
Synonyms: Isopropyl alcohol, 2-propanol, secondary propyl alcohol, dimethyl carbinol, Perspirit, Petrohol, Avantine, IPA

Isopropanol, $(CH_3)_2CHOCH$,is a colorless liquid with a pleasant ordor similar to that of an ethanol/acetone mixture. Its molecular weight is 60.09. The melting point of isopropanol is -89.5 C; the boiling point is 82.4°C. Isopropanol is miscible with water, alcohol, ether, and chloroform. Isopropanol and water form an azeotrope with a boiling point of 80.4 C (87.7% isopropanol, w/w). The specific gravity of isopropanol is 0.7863 at 20°C; the vapor pressure is 33 mm Hg (Hawley, 1977).

## Health Aspects

NIOSH estimates that approximately 141,000 employees are potentially exposed to ispropyl alcohol (NIOSH, 1976). OSHA has set the time-weighted average exposure at 400 ppm (NIOSH, 1977). Nelson et al. (1943) exposed human subjects to various concentrations of isopropanol to determine what level can be tolerated in the workplace. The highest concentration which the majority of the subjects estimated would be satisfactory for an 8-hour exposure was 200 ppm. This is also the level where the subjects were first able to detect the presence of isopropanol. At 400 ppm there was mild irritation of eyes, nose, and throat, but no narcosis.

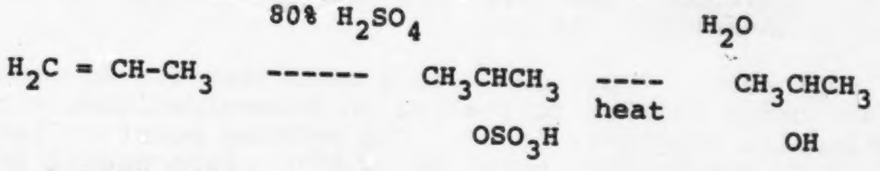
The chemical activity of isopropyl alcohol is primarily associated with the hydroxyl group. As a secondary alcohol its reactivity differs in a number of important ways from primary alchols, for example, in ease of conversion to ethers and esters, and in the formation of products obtained by oxidation and catalytic reactions. It does, however, undergo many of the reactions typical of the lower molecular weight primary alcohols. It reacts readily with metals such as sodium and potassium and it forms halides by reacting with the corresponding halogen acid.

$$CH_3CHOHCH_3 + HX \text{ -- } CH_3CHXCH_3 + H_2O$$

(Kirk-Othmer, 1968).

## Processing Methods

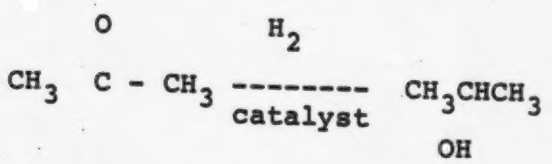
Isopropanol is usually made from propylene, a by-product in the cracking of heavy petroleum hydrocarbons. The addition of sulfuric acid to propylene forms propyl sulfate which is hydrolyzed to isopropanol.



$$H_2C = CH\text{-}CH_3 \xrightarrow{80\%\ H_2SO_4} \underset{OSO_3H}{CH_3CHCH_3} \xrightarrow[heat]{H_2O} \underset{OH}{CH_3CHCH_3}$$

(Morrison and Boyd, 1970).

Isopropanol is also produced by the catalytic hydrogenation of acetone.



$$CH_3\ \overset{O}{C} - CH_3 \xrightarrow[catalyst]{H_2} \underset{OH}{CH_3CHCH_3}$$

(EPA, 1978)

Isopropanol is available in three grades: 99%, 95%, and 91% (Hawley, 1977).

Table 1. Major Manufacturers of Isopropanol and Their Production Levels.

| Method of Production | Company | Locations | Tons/yr. |
|---|---|---|---|
| Continuous hydrolysis of propylene | Union Carbide Corp. | Charlestown, WV | 38,873 |
| | Union Carbide Corp. | Texas City, TX | 262,800 |
| | Exxon Corp. | Baton Rouge, LA | 472,675 |
| | Shell Oil Co. | Deer Park, TX | 299,300 |
| | Union Carbide Corp. | Texas City, TX | 195,275 |
| | Shell Oil Co. | Carson, CA | 33,033 |
| Catalytic hydrogenation of acetone | ARCO Chemical Co. | Channelview, TX | 9,344 |
| Solvent-water azeotropic distillation | Eastman Kodak Co. | Kingsport, TN | 73,000 |
| TOTAL | | | 1,384,300 |

Source: EPA, 1978.

## Production and Use

Isopropanol is included in many commercial products such as liniments, lotions, cosmetic, perfumes, hair tonics, permanent wave preparations, pharmaceuticals, antifreezes, liquid soaps and window cleaners. It is used as a preservative in nitrocellulose lacquer formulations and dye solutions, as a coupling agent in oil emulsions, and as an extracting agent for sulfonic acids from petroleum oils (Patty, 1963). More than 50% of the isopropanol manufactured is used as a raw material in the production of acetone (NIOSH, 1976). It is most popularly known to consumers as rubbing alcohol, a solution of 70% isopropanol and 30% water.

No recorded cases of industrial poisoning by pure isopropyl alcohol by any route were found in the literature. However, toxicity due to simultaneous exposure to carbon tetrachloride and isopropanol has occurred in the workplace. Fourteen workers in an isopropyl alcohol packaging plant became ill after accidental exposure to carbon tetrachloride. Renal failure or hepatitis developed in four cases. Acetone, a product of isopropanol metabolism, is a major potentiator of carbon tetrachloride toxicity. Workers had elevated levels of acetone in samples of expired alveolar gas and were, therefore, predisposed to carbon tetrachloride injury. Stricter limits for industrial exposure to $CCl_4$ were recommended in cases where isopropyl alcohol is also found in the work environment (Folland et al., 1976).

Many cases of ingestion of rubbing alcohol have been reported. This does not seem to be as prevalent as the ingestion of methanol by chronic alcoholics, but Adelson (1962) reported five fatal cases that occurred over a seven year period. All five cases were reported to have consumed approximately 1 pint of rubbing alcohol. The common symptom of the intoxication was a deep coma with marked depression leading to an absence of reflexes. Most acute exposures led to rapid death via central nervous system depression resulting in respiratory paralysis. One man lived for 15 days after drinking 1 1/3 pints of rubbing alcohol. He suffered from ischemic muscular necrosis, upper gastrointestinal bleeding and kidney failure. He died despite four episodes of peritoneal dialysis.

Peritoneal dialysis has been recommended to treat acute isopropanol intoxication especially if hemodialysis is not available (Dua, 1974). Gleason (1969) reports a case where a man drank one quart of rubbing alcohol and survived after undergoing hemodialysis.

Isopropanol is generally considered to be twice as toxic as ethanol, but less toxic than methanol. Its major metabolite is acetone (Gleason, 1969). The symptoms of isopropanol poisoning follow: 1) Dizziness, incoordination, headache, confusion, stupor and coma; 2) gastroenteritis with vomiting, hematemesis, and diarrhea; 3) hypotension, with or without bradycardia, and sometimes severe circulatory collapse; 4) persistent coma with hypothermia; 5) death by respiratory arrest; and 6) late manifestations: aspiration pneumonia; kidney and liver dysfunction which are usually mild and transient by may be serious (Gleason, 1969).

Wills (1969) ran a study using human subjects to determine the effects of daily ingestions of small doses of isopropanol. Groups of 8 men drank a placebo, 2.6 mg/kg or 6.4 mg/kg of isopropanol daily for 6 weeks. No changes were seen in blood or urine, optical properties of the eye, or the ability of the liver to excrete sulfobromophthalein (an indication there was no liver damage).

There have been a number of cases reported where children developed comas after topical applications of isopropanol to reduce high fevers. A 2 1/2 year-old girl was wrapped in a towel saturated with isopropanol (12 ounces) and a dry towel was placed over the first. Eight hours later she was limp and totally unresponsive. This was believed to be caused by inhalation of isopropanol (Senz, 1958).

Some people have an allergic reaction to skin contact with isopropanol. The injection site on one woman's arm was cleansed with an isopropanol swab prior to injection. Subsequently she held the swab against the site for about 2 minutes. A rash developed at the injection site and on her fingers. Bullous lesions developed and had to be drained twice. The condition did not completely clear up until 21 days later (Wasilewski, 1968).

## Animal Exposure

The oral $LD_{50}$ of isopropanol in rats, rabbits and dogs is 6-7 gm/kg. By intravenous injection, the anesthetic dose in rabbits and dogs is 3.3 cc/kg and the fatal dose is 8.2 and 5.1 cc/kg respectively. In a 27 week study, rats were given isopropanol in their drinking water in solutions ranging from 0.5% to 10%. Rats refused to drink the 10% solution and died after 7 to 28 days. The 1% and 5% groups remained well but did experience retardation of growth and body weight loss (Lehman and Chase, 1944). Boughton (1944) provided a 5% solution of isopropanol as the only water supply to a group of rats for nine months. The rats experienced marked weight depression and noisy breathing, both of which disappeared after the administration of isopropanol was stopped. The rats were also sluggish in the maze runs. There was no difference in the death rate between these rats and controls. Isopropanol was also applied to the face area of the rats. After 187 applications of a 50% solution, no injury was seen in the skin, hair or eyes.

## Carcinogenicity Studies

During the 1940's, epidemiological evidence raised suspicion that there was a carcinogen present in the production of isopropanol (Weil, 1952). Seven neoplasms of the respiratory tract were discovered in an isopropanol production unit between 1937 and 1950. Detailed studies of the medical and employment records of the unit showed that cancer of the respiratory tract developed in 8.4% of employees exposed for more than five years. Animal studies on isopropanol and the other chemicals present in the air of the production unit were conducted to determine which was responsible for the tumors. Several strains of mice were used for inhalation and subcutaneous injection experiments. Isopropyl oil (polypropylene and very small amounts of benzene) toluene, alkyl benzenes, polyaromatic rings, hexane, acetone, ethanol, isopropanol, and isopropyl ether, gave positive results by both subcutaneous injection and mist inhalation. The incidence of tumors in mice exposed to isopropanol was no different from that of the controls. The author concludes that isopropanol is not a carcinogen and isopropyl oil may have been the human carcinogenic agent in the isopropanol production process.

## Environmental Aspects

The BOD of isopropanol is 78% of the theoretical after 20 days at 20°C (total theoretical demand is 2.4 g/g) (Verschueren, 1977). An estimated 50% of isopropanol is eventually dispersed with an additional 1.5% lost in production. The release rate would be roughly 876 million l/year if consumption were 1,698 million l/year (Dorigan et al., 1976).

The lethal concentrations of isopropanol to fathead minnows in Lake Superior waters were determined (EPA, 1976).

$LC_{50}$ (mg/l)

| 1-hr | 24-hr | 48-hr | 72-hr | 96-hr |
|---|---|---|---|---|
| 11.830 | 11,160 | 11,130 | 11,30 | 11,130 |

Creek chub fish were exposed to isopropanol is Detroit river water. After 24 hours, no fish died at 90 mg/l and all fish were killed by 1,000 mg/l. The 24-hour $LC_{50}$ in gold fish is greater than 5,000 mg/l (Verschueren, 1977).

| Species | Inhibition of Cell Multiplication | Toxic Level |
|---|---|---|
| Pseudomonas Putida (bacteria) | 1050 mg/l | |
| Chlorella Pyrenaidosa (algae) | | 17,000 mg/l |
| Microcystis aeruginosa (algae) | 1000 mg/l | |
| Brown Shrimp | | $LC_{50}$(48 hr) 1400 mg/l<br>$LC_{50}$(96 hr) 1150 mg/l |

Source: Adapted from Verschueren, 1977.

## REFERENCES

Adelson, L. Fatal intoxication with isopropyl alcohol (rubbing alcohol). Am. J. Clin. Pathol. 38, 144-151, 1962.

Boughton, L.L. The relative toxicity of ethyl and isopropyl alcohol as determined by long-term rat feeding and external application. J. Am. Pharm. Assoc. 33, 111-113, 1944.

Dorigan, J. et al. Scoring of Organic Air Pollutants: Chemistry, Production, and Toxicity of Selected Organic Chemicals. MITRE Corp. 1976.*

Dua, S.L. Peritoneal dialysis for isopropyl alcohol poisoning. J. Am. Med. Assoc. 230(1), 35, 1974.

EPA, Office of Research and Development EPA-600/3-76-097. Acute toxicity of selected organic compounds to fathead minnows, 1976.

EPA, EPA Guidelines Report, Plants by Product Process, Oct. 1978.

Folland, D.S. et al. Carbon tetrachloride toxicity potentiated by isopropyl alcohol. J. Am. Med. Assoc. 236(16), 1853, 1976.

Fregert, S. et al. Alcohol dermatitis. Acta Derm. Venereol. 49, 493-497, 1969.

Fuller, H.C. and O.B. Hunter. Isopropyl alcohol - an investigation of its physiologic properties. J. Lab Clin. Med. 12, 326-349, 1927.

Garrison, R.F. Acute poisoning from use of isopropyl alcohol in tepid sponging. J. Am. Med. Assoc. 152, 317, 1953.

Gibel, W. et al. (Experimental studies on the carcinogenic effect of higher alcohols using 3-methyl-1-butanol, 1-propanol and 2-methyl-1-propanol as examples.) Zeitschrift fur Experimentelle Chirurgie 7(4), 235-239, 1974.

Gleason, M.N. et al. Clinical Toxicology of Commercial Products, 3rd ed. Baltimore, MD, Williams and Wilkins Co., 1969.

Hawley, G.G. (ed.) . Condensed Chemical Dictionary, 9th ed. New York, Van Nostrand Reinhold Co., 1977.

Hillbom, M.E. et al. Effects of chronic ingestion of some lower aliphatic alcohols in rats. Research Communications in Chemical Pathology 9(1), 177, 1974.

Hodge H.C. and W.L. Downs. The approximate oral toxicity in rats of selected household products. Toxicol. Appl. Pharmacol. 3, 689-695, 1961.

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*This document was prepared for the U.S. Environmental Protection Agency by the MITRE Corp. It is a secondary source and does not cite its primary references. Thus, verification of some information is not possible. The environmental release data were taken from the NSF/Rann Research Program on Hazard Priority Ranking of Manufactured Organic Chemicals.

International Technical Information Institute. Toxic and Hazardous Industrial Chemicals Safety Manual. Tokyo. 1976.

Juncos, L. and J.T. Taguchi. Isopropyl alcohol intoxication - Report of a case associated with myopathy, renal failure, and hemolytic anemia. J. Am. Med. Assoc. 204, 732-734, 1968.

June, C.H. Alcoholic ketoacidosis and isopropyl alcohol intoxication. Arch. Intern. Med. 138, 660, 1978.

Kirk-Othmer Encyclopedia of Chemical Technology, 2nd ed., Vol. 16. Anthony Standen, executive editor. New York, John Wiley and Sons, Inc. 1968.

Lehman, A.J. and H.F. Chase. The acute and chronic toxicity of isopropyl alcohol. J. Lab Clin. Med 29, 561-567, 1944.

Macht, D.I. Pharmacological Examination of Isopropyl Alcohol. Arch. Int. Pharmacodyn Ther. 26, 285-289, 1922.

McCord, W.M. et al. Isopropyl alcohol intoxication. South Med. J. 41, 639, 1948.

McFadden, S.W. and J.E. Haddow. Coma produced by topical application of isopropanol. Pediatrics 43, 622-623, 1969.

McInnes, A. Skin reaction to isopropyl alcohol. Br. Med. J. 1, 357, 1973.

The Merck Index, 8th ed. Rahway, N.J., Merck and Co., Inc. 1968.

Morris, H.J. and H.D. Lightbody. The toxicity of isopropanol. J. Ind. Hyg. Toxicol. 20, 428-434, 1938.

Morrison, R.T. and R.N. Boyd. Organic Chemistry, 2nd ed. Boston, Allyn and Bacon, Inc. 1970.

Nelson, K.W. et al. Sensory response to certain industrial solvent vapors. J. Ind. Hyg. Toxicol. 25, 282-285, 1943.

NIOSH. Criteria for a recommended standard...Occupational exposure to isopropyl alcohol. March 1976.

NIOSH. Registry of Toxic Effects of Chemical Substances. 1977.

Patty, F.A. (ed.). Industrial Hygiene and Toxicology, 2nd ed. New York, Interscience Publishers, Inc. 1963.

Plaa, G.L. et al. Effect of alcohols on various forms of chemically induced liver injury. Alcohol Liver Pathology (Proceed-ings of the International Symposium on Alcohol and Drug Research). 1975.

Richardson, D.R. et al. Allergic Contact Dermatitis to "Alcohol" Swabs. Cutis 5. 1115-1118, 1969.

Sanz, F. et al. (Standards for the study of teratogenic and embryopathic action in dogs.) Arch. Inst. Farmacol Exp. (Madr) 22(1-2), 7-11, 1970.

Sax, N. Irving (ed.). Dangerous Properties of Industrial Materials, 3rd, ed. New York, Van Nostrand Reinhold Co. 1968.

Senz, E.H. and D.L. Goldfarb. Coma of a child following use of isopropyl alcohol in sponging. J. Pediatr. 53, 322-323, 1958.

Van de Graaff, W.B. and W.L. Thompson. Isopropyl alcohol intoxication. Arch. Intern. Med. 138(5), 826, 1978.

Vasiliades, J. et al. Pitfalls of the alcohol dehydrogenase procedure for the emergency assay of alcohol: A case study of isopropanol overdose. Clinical Chemistry 24(2), 383, 1978.

Verschueren, K. Handbook of Environmental Data on Organic Chemicals. Litton Educational Publishing, Inc. 1977.

Wasilewski, C. Allergic Contact Dermatitis from Isopropyl Alcohol. Arch. Dermatol. 98, 502-504, 1968.

Weil, C.S. et al. Quest for a suspected industrial carcinogen. Arch. Ind. Hyg. Occup. Med. 5, 535-547, 1952.

Wills, J.H. et al. Effects on man of daily ingestion of small doses of isopropyl alcohol. Toxicol. Appl. Pharmacol. 15, 560-565, 1969.

# CHEMICAL HAZARD INFORMATION PROFILE

## Lithium and Lithium Compounds

Date of report: September 1, 1976

This group of compounds was chosen for study because of its known effects on the nervous system and its suggested use as an additive to drinking water.

Lithium and lithium compounds are not recommended for priority evaluation within OTS at this time. None of the available information indicates that these substances pose a hazard to human health or the environment.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

## Chemical Identity

Lithium is the third lightest element and lightest of all the metals, with an atomic number of 3 and an atomic weight of 6.939. The density of pure lithium is 0.531 g/ml. It melts at 180.5¼C and boils at approximately 1,326 °C. Lithium is present as a trace element in many minerals, and makes up about 0.005% of the earth's crust. Minerals richest in lithium are spodumene, $LiAlSi_2O_6$; petalite, $LiAlSi_4O_{10}$; lepidolite, a complex mica; and amblygonite, $LiAlFPO_4$. Lithium is the hardest alkali metal, but is still very soft, rating 0.6 on the Mohs scale as compared with 10 for diamond and 1 for graphite. Lithium is present naturally as two isotopes: lithium-6, making up 7.39% of natural lithium, and lithium-7, comprising the remaining 92.61%. Lithium-6 has the ability to gain a neutron, which converts it to the heavier isotope. Lithium has the highest heat capacity of any element in both liquid and solid phases: 0.83 cal/g°C at 25°C and 1.37 cal/g°C at 190°C. It is a very reactive metal, combining spontaneously with nitrogen, hydrogen, and water, and when heated will burn in the air. Unlike other alkali metals, the reaction with water is not violent enough to ignite the hydrogen evolved. Lithium can form covalent bonds to carbon, and reacts with most organohalides to form organolithium compounds. Lithium ions will form ionic salts with a wide range of anions. Some of the more important compounds are outlined below.

Lithium acetate, commonly used as the dihydrate, $CH_3COOLi \cdot 2H_2O$, is a white crystalline powder that will dissolve in either water or alcohol. The dihydrate melts at 58°C in its water of hydration, while anhydrous lithium acetate melts at 291°C.

Lithium aluminum hydride, $LiAlH_4$, is a white crystalline powder. It is stable in dry air at room temperature, but will decompose in moist air or at temperatures above 125°C. It is soluble in ether and reacts violently with water or alcohol. It is a common laboratory reducing agent, active on carbonyl groups as in aldehydes, ketones, and acid chlorides, but will not reduce olefinic double bonds.

Lithium amide, $LiNH_2$, forms cubic crystals that are insoluble in anhydrous ether, benzene, or toluene. It begins to decompose at 320°C and melts at about 375°C.

Lithium borates form a number of different crystalline powders that are slightly soluble in water and insoluble in alcohol. Anhydrous lithium metaborate, $LiBO_2$, melts at 849°C, while the tetraborate, $LiB_4O_7$, melts at 917°C.

Anhydrous lithium bromide, LiBr, is a white granular powder melting at 547°C and boiling at 1,310°C. It is quite hygroscopic and will dissolve in water, alcohol, glycol, and ether.

Lithium carbonate, $Li_2CO_3$, is the salt with the highest lithium content by weight. It is a white powder that is slightly soluble in water and soluble in alcohol. It begins to decompose at temperatures above 600°C.

Lithium chloride, LiCl, a crystalline powder, will dissolve readily in water, alcohol, acetone, and pyridine. Anhydrous lithium chloride is very hygroscopic. A sample left open to the air will dissolve in the water it adsorbs. The melting point of the anhydrous salt is 608°C, and the boiling point is 1,382°C.

Lithium fluoride, LiF, melts at 848°C and boils at 1,681°C. It forms either cubic crystals or a fluffy white powder. It is insoluble in water, but will dissolve in acid solutions.

Lithium formate monohydrate, $HCOOLi \cdot H_2O$, forms water-soluble white or colorless crystals. When heated, the substance loses water at 100°C and decomposes at about 230°C.

Lithium hydride, LiH, forms cubic crystals that melt at 680°C. It is an excellent source of gaseous hydrogen. One pound of lithium hydride will react vigorously with water to release 45 $ft^3$ of hydrogen. It undergoes many of the reactions of elemental lithium and will only reduce such easily reduced organics as acid chlorides.

Lithium hydroxide, LiOH, is a white granular powder. Anhydrous lithium hydroxide melts at 471°C and will dissolve readily in water and slightly in alcohol. It will adsorb water or carbon dioxide from the air.

Lithium iodide, LiI, will form a number of hydrated salts. The trihydrate melts at 75°C, the dihydrate at 79°C, and the monohydrate at 130°C. Anhydrous lithium iodide, a white granular powder, melts at 469°C and boils at 1,142°C. It is sparingly soluble in water and alcohol and dissolves easily in acetone.

Lithium nitrate, $LiNO_3$, melts at 251°C. Its colorless granules will dissolve in either water or alcohol.

Lithium oxide is a white powder that remains solid at temperatures up to 1,700°C. Like lithium hydroxide, it is a very efficient $CO_2$ adsorbent and will also adsorb water from the atmosphere.

Lithium metasilicate forms orthorhombic needles that melt at 1,201°C. It is insoluble in water.

Organolithium compounds are very useful in preparative organic chemistry because of the polar-covalent nature of the carbon-lithium bond. They are highly reactive with $CO_2$ and $O_2$ but not $N_2$, and burn spontaneously in air. The most important commercial species is n-butyl lithium.

## Production

The most extensively mined lithium ore is spodumene, although rich enough deposits of any lithium mineral could be utilized. There are a large number of processes in use for the extraction of lithium, but they are all variations of essentially two processes. In one, ground spodumene and limestone are mixed and fired to 1,100°C. The resultant clinker is ground and hot-leached with water, yielding impure lithium hydroxide solution which is concentrated, filtered, and recrystallized to purity. In the other process, ground spodumene is heated at about 110°C to convert it from the alpha to the more active beta form. This is ground and mixed with hot sulfuric acid. Hydrogen replaces lithium in the mineral, yielding soluble lithium sulfate. After filtration to remove the insoluble residue, sodium carbonate is added to the liquor to precipitate lithium carbonate, which is then purified by washing and recrystallization. Lithium can also be separated from brines, though this is not commercially feasible in most cases unless produced as a by-product in the separation of salts such as potash or borax. The by-product waste brines are treated with hot sulfuric acid to separate the alkali sulfates. Sodium carbonate is added to precipitate lithium carbonate. Lithium carbonate is produced as the main product in Silver Peak, Nev., where the brine has an unusually high Li content of 300 ppm.

Lithium salts such as the acetate, bromide, chloride, fluoride, formate, iodide, nitrate, or sulfate can be made by mixing lithium carbonate or hydroxide with aqueous solutions of the appropriate acid. Ammonia gas will combine with hot lithium metal to produce the amide. Lithium carbide and hydride can be produced by direct combination of the heated component elements. Lithium hydroxide solution and hydrogen peroxide yield lithium peroxide, and the calcination of lithium carbonate with silica yields lithium metasilicate. Organolithium compounds are prepared by reacting finely divided metallic lithium in mineral oil with the appropriate organohalide.

Pure lithium metal is commercially produced by electrolysis using a 55 wt% LiCl/45 wt% KCl electrolyte at temperatures of about 460°C. Using a low-carbon steel cell and a graphite rod anode, about 98% of the lithium can be recovered at a purity of at least 99.8%. Lithium metal is marketed in 1/4-, 1/2-, 1-, and 2-lb ingots, ribbon, wire, rod, and shot, and as dispersions in mineral oil.

No data on the production or consumption of lithium and lithium compounds are available from the literature. Production of lithium in 1968 has been estimated at 2,900 tons for the United States and 4,700 tons for the world (Mineral Facts and Problems, 1970). The growth rate is expected to parallel that of the gross national product.

Major producers of lithium and lithium chemicals include Foote Mineral Co., Lithium Corporation of America, and Harshaw Chemical Co.

## Use

Lithium metal loses its extreme reactivity when combined with other metals into alloys. When combined with aluminum, lithium greatly increases the tensile strength of the material. Lithium-magnesium alloys have the highest strength/weight ratio of any structural metal. One alloy, LA141, containing 85% magnesium, 14% lithium, and 1% aluminum, has found extensive applications as a structural material in the aerospace industry. Lithium was used as a fuel for the first series of hydrogen atomic bombs. Because of the high reactivity of lithium with oxygen and nitrogen, it has found use in metallurgy as a degasser and scavenging agent in molten metal. Potential future uses for lithium metal include utilization as the anode in high-energy batteries, as in electric cars. The expansion of the atomic power industry will also provide applications. Because of its ability to absorb stray neutrons, lithium-6 would make an excellent radiation shield for nuclear reactors. Its high heat capacity would also make lithium an ideal heat exchange medium for such thermonuclear reactors. The chief problem for this application has been to find a container with which molten lithium will not react.

Lithium acetate is used in organic synthesis, especially in the preparation of medicinal formulations. It is a good catalyst for the alcoholysis route of alkyd resin manufacturing.

Lithium aluminum hydride is a common laboratory reducing agent, and also finds use in the preparation of other hydrides.

Lithium amide is used extensively in the pharmaceutical industry for the synthesis of antihistamines. It is also used in Claisen condensations, alkylations of nitriles and ketones, and the synthesis of ethynyl compounds and acetylenic alcohols.

Lithium borates are used in the ceramics industry and in the formulation of special-purpose glasses and enamels. Lithium metaborate is also used as the matrix material for X-ray spectroscopy.

Lithium bromide is used in the laboratory as a catalyst and dehydrohalogenating agent. It was used briefly in medicine as a hypnotic and sedative. Anhydrous lithium bromide is used as a dehumidifier in air conditioning systems, and 54-55% lithium bromide brine is similarly utilized in adsorption refrigeration systems.

Lithium carbonate is the starting material for the preparation of many other lithium salts. It finds use in the ceramics industry for the formulation of various enamels, glasses, and glazes. More recently, lithium carbonate has been used in the treatment of manic-depressive psychosis and other types of psychological illnesses.

Lithium chloride is the raw material for the production of lithium metal. It is also used in brazing fluxes, as an electrolyte for low-temperature dry cells, and as a dehumidifier in air conditioning systems.

Lithium fluoride is used as a brazing and welding flux as well as in the preparation of enamels, glasses, and glazes. It also finds special applications in molten bath chemistry.

Lithium hydride is a very efficient source of gaseous hydrogen and as such has been used as a compact source of lighter-than-air gas for balloons. Many of the applications of lithium metal also apply to lithium hydride; it can be used as a heat sink and a shield for thermal neutrons.

Lithium hydroxide, like lithium carbonate, can be converted to other lithium salts. Its most important use is in the manufacture of lithium stearate or other lithium soaps. These soaps are combined with lubricating oil at a ratio of 1 part soap to 9 parts oil to produce grease that retains its desired properties in a temperature range of -52° to 138°C. Lithium hydroxide is used as an atmosphere-regenerating agent because of its ability to adsorb carbon dioxide. It is also used as an electrolyte in alkaline storage batteries.

Lithium hypochlorite, with 35% available chlorine, is used as a sanitary agent for swimming pools and as the active ingredient in a few laundry bleaches.

Lithium nitrate is used as a flame colorant in fireworks and flares and as an etchant in glass manufacture.

Lithium oxide, like lithium hydroxide, is a very efficient adsorbent for carbon dioxide and can be similarly used as an air purifier.

Lithium peroxide is a more efficient atmosphere regenerator than either lithium hydroxide or oxide since it contains 35% active oxygen which is released upon reaction with carbon dioxide.

Lithium sulfate is used in glass formulations to produce glass for special applications requiring extra strength.

Organolithium compounds are very useful and versatile tools in organic synthesis, especially in the anionic polymerization of conjugated dienes. They are used commercially to produce the synthetic rubber polyisoprene.

## Health Aspects

There is no information in the literature concerning any biological effects of lithium metal. However, because of its high reactivity with water, any contact with living tissue will produce deep burns. Organolithium compounds are similarly highly reactive and should be handled with extreme care.

The preponderance of studies on the biological effects of lithium compounds are related to its therapeutic use in psychiatric medicine. This aspect of lithium is summarized in the appendix.

The following are toxic and lethal doses of lithium chemicals to various organisms listed by the Registry of Toxic Effects of Chemical Substances:

| Substance | Route | Organism | Dose (mg/kg) |
|---|---|---|---|
| Lithium | Intraperitoneal | Pregnant rat | $TD_{10}=360$ |
| Lithium carbonate | Oral | Human | $TD_{10}=7$ |
| | Oral | Rat | $TD_{10}=710$ |
| | Oral | Pregnant rat | $TD_{10}=300$ |
| | Oral | Dog | $TD_{50}=300$ |
| Lithium chloride | Oral | Rat | $LD_{50}=757$ |
| | Oral | Rabbit | $LD_{90}=850$ |
| | Parenteral | Pregnant rat | $TD_{10}=1{,}062$ |
| | Intraperitoneal | Mouse | $LD_{50}=604$ |
| | Subcutaneous | Mouse | $LD_{10}=2{,}000$ |
| Lithium fluoride | Oral | Guinea pig | $LD_{10}=2{,}000$ |
| | Subcutaneous | Guinea pig | $LD_{10}=2{,}000$ |
| | Subcutaneous | Frog | $LD_{10}=280$ |

$TD_{10}$ = lowest published toxic dose.
$LD_{10}$ = lowest published lethal dose.
$LD_{50}$ = lethal dose, 50% kill.
$LD_{90}$ = lethal dose, 90% kill.

An interesting correlation has been found between the lithium content of drinking water and the death rate due to atherosclerotic heart disease, both in the United States (Blachly, 1970) and in Britain (Polumbo et al., 1973). The lithium levels in water of cities with the lowest fatality rates approach that of seawater. Lithium diminishes five major atherosclerotic heart disease risk factors: hypertension, diabetes mellitus, uric acid levels, hypomanic behavior, and serum lipid levels (Voors, 1969), and has also been shown to relieve ouabain-induced cardiac arrhythmias in dogs (Polumbo et al., 1973). The protective effect of lithium seems clear and may indicate that it is a vital element.

There has been some concern about the use of lithium during human pregnancy, because of scattered data concerning the teratogenicity of lithium in lower species. Lithium disrupts normal blastulation in sea urchins (Gustafson and Lenicque, 1952), and at concentrations above 75 ppm produces significant decreases in survival rates of bass embryos (unpublished data from University of Kentucky, 1975). Lithium at 1:300 parts in growth medium of frog eggs for 6 hr produces irreversible and lethal morphological damage during gastrulation (Blando-Hoegler, 1974). In the culture medium of Drosophila (fruit flies), 0.022 M lithium was lethal to all developing eggs (King, 1953). Rats, rabbits, and rhesus monkeys receiving up to 4.05 mEq/day orally during organogenesis produced completely normal offspring (Gralla and McIlhenny, 1972). However, pregnant mice exposed to lithium for the first 10 days of pregnancy at levels approximating those used therapeutically produced significantly smaller litters than controls and several offspring with cleft palate. No other types of abnormalities were found (Szabo, 1970). In another experiment, pregnant goats were infused with lithium chloride to yield blood levels of 4.90 mg/ml. Seventy-five percent of the offspring were aborted and showed complete liver degeneration, while those surviving showed hepatic degeneration and necrosis (Boulos et al., 1973). A register of lithium babies has been set up, and the results to date indicate that the total rate of abnormalities is not significantly different from a normal population, but that the rate of congenital heart disease and the ratio of cardiovascular defects to total defects appear high (Weinstein and Goldfield, 1975).

Lithium, when added to culture medium of sugar beets at 1 mEq/l, produces growth stunting of shoots and fibrous roots. At 8 mEq/l, the leaves begin to grow yellow and curl up. The mechanism for the toxic effect is believed to be competitive inhibition of potassium and calcium absorption (El-Sheikh et al., 1971). Lithium at 10-100 mM has been reported as toxic to tomato plants (Kabanov and Myasoedov, 1974), but at lower concentrations it aids photosynthesis and respiration in tobacco plants (Ezdakova, 1962).

## Environmental Aspects

Lithium makes up 0.005% of the earth's crust. Where it is present in the soil as a result of degradation of lithium-containing minerals, lithium ions are leached from the soil by rainfall and enter the ground water and thus, ultimately, the water supply. There are amounts of lithium released into the water systems as wastes from industrial processes producing or utilizing lithium chemicals. There is no evidence that any abnormally high levels of lithium in the environment have resulted. Analysis of water supplies in Texas yielded values for the lithium concentration of 0.001 to 0.078 mg/l. The most concentrated lithium brine known contains 300 mg/l. There is virtually no danger that toxic amounts of lithium could be ingested from environmental sources. Any effects on human health from environmental encounters appear to be beneficial, and lithium enrichment of drinking water has been suggested. Lithium is not known to undergo bioaccumulation in any organism.

## APPENDIX

### Psychiatric Uses of Lithium

Ever since Cade reported in 1949 that lithium could relieve a manic episode in manic-depressive-type psychotic patients, a great deal of research has been going on concerning the psychoactive and metabolic effects of lithium ions. It was hoped that from this research would come a better understanding of the nature of mania and depression, but thus far the metabolic effects of lithium appear to be as numerous and varied as the mental conditions that it affects. This research has the potential to explain a great deal about the nature of emotion if all the connecting factors can be determined, but thus far the evidence has supported no particular hypothesis.

The greatest part of the research on the biological properties of lithium is being directed toward manic-depressive psychosis. Obtaining firm results as to the efficacy of lithium in treating any mental disease is difficult due to the problems in firm diagnosis and in running well-controlled double-blind experiments. However, it appears that the effectiveness of lithium in halting acute mania is somewhere between 75 and 100% 1 to 2 weeks after the initiation of treatment. The evidence concerning lithium as treatment in acute depressive episodes is less clear, but some positive effects seem likely, especially when the episode is part of a true cyclic manic-depressive disorder. Even more interesting is the evidence that lithium has a prophylactic action in preventing recurrent episodes, both in manic-depressive psychosis and in unipolar recurrent depression (Tupin, 1970). In these effects lithium is unique among drugs, especially so in that there is no psychological effect of sedation or any other disruption of thought. However, cases have been reported where lithium has had a negative effect on manic-phase creative output during hypomania (Polatin, 1972).

Because of the status of lithium as somewhat of a "wonder drug," it has been used in other types of mental disorders. However, most of the evidence is in the form of individual case reports, so no firm conclusions can be drawn. Lithium has been reported to cure the affective or manic-type hyperactivity in schizo-affective disorders. It also supposedly prevents premenstrual tension, some types of childhood and adolescent personality disorders, and some cases of psychomotor epilepsy (Tupin, 1970). Cases of particularly dramatic recovery have been reported in explosively aggressive, often criminal, individuals (Sheard, 1971). Two common characteristics of many of these disorders are aggressiveness and an episodic-repetitive course.

In spite of the amount of research that has been done on lithium and manic-depressive psychosis, very little is understood about either of them. The major problem is that the effects lithium produces on the body are so numerous that those related to psychologic activity cannot be distinguished from the irrelevant side effects. As a result, a number of hypotheses have arisen, all of which are both somewhat supported and refuted by the evidence at hand. These hypotheses fall into three general types. One says that mania and depression are caused by the same dysfunction and that one is an extreme form of the other. Another outlook views the two problems as causing one another and being so closely related that curing one prevents the other from recurring. A third approach claims that mania and depression and the effects of lithium on them are separate and not related. The major effects of lithium on the body and some of the ideas these observations have evoked are presented here.

Lithium ions have been observed to slow down the circadian rhythm of a species of flowering plant and a small mammal. The similarity of the manic-depressive cycle and its relation to the human circadian cycle are called to attention as one explanation of the therapeutic action of lithium (Englemann, 1973).

One natural area for observation on the effects of any psychoactive drug is neurotransmitter metabolism. Lithium acts to increase neuronal turnover and metabolic degradation of norepinephrine, a neurotransmitter commonly believed to have an excretion increase during mania and decrease in depression, which may or may not be an indication of central nervous system (CNS) activity. Lithium decreases the availability of norepinephrine at the receptor site and tends to increase the rate of its metabolic degradation. These actions would explain the effect of lithium on mania but not on depression (Andreasen, 1971). However, it has also been proposed that the central nervous system is in a state of hyperexcitability in depression as well as during mania (Mellerup and Rafaelson, 1974). When exogenous quantities of norepinephrine are made available to the CNS, the effect is sedation rather than excitement (Ketu, 1972). Thus, administration of lithium to manic or depressed patients could be curing different degrees of the same problem. The effects of lithium on serotonin, a CNS neurotransmitter whose role in psychological illness is not known, are contradictory. The rates of both synthesis and degradation are increased, with increased synthesis predominating (Schubert, 1973; Perez-Cruet, 1971). Lithium is also believed to block synthesis of acetylcholine, a peripheral neurotransmitter (Vizi et al., 1972).

The mode of action by which lithium interferes with the action of many hormones and metabolically active chemicals, including serotonin and norepinephrine, is through inhibition of the enzyme adenylate cyclase. This enzyme catalyzes the production of cyclic adenosine monophosphate (CAMP), which appears to be a directly active chemical that mediates the action of many hormones (Singer and Rotenberg, 1973). The blocking of this pathway is responsible for many of the observed effects of lithium, and could be the explanation of its antipsychotic effect.

Another observed side effect of lithium use is polydipsia or excessive thirst and a lack of urine concentrating ability. Administration of vasopressin, or antidiuretic hormone (ADH), which increases the water reabsorbed by the kidney, has no effect on this condition. This can be explained by the inhibition by lithium of adenylate cyclase, since the action of ADH on the renal concentrating mechanism is mediated by CAMP (Singer and Rotenberg, 1973).

Under the influence of lithium, levels of glucagon, a hormone stimulating breakdown of glycogen in the liver, increase, resulting in a decrease in liver glycogen and increased levels of glucose in the blood. Hepatic synthesis of cholesterol and triglycerides also drops (Singer and Rotenberg, 1973). Accompanying the rise in circulatory glucose is increased uptake of glucose by brain, muscle, and adipose tissue and conversion to glycogen (DeFeudis, 1973). This explains the weight gain often observed in lithium-dosed patients.

Lithium has also been reported to cause dramatic rises in white blood cell (WBC) counts. In manic patients treated with lithium, WBC counts rose from averages of 9,000 to 12,000, while WBC counts in depressed subjects saw average increases from about 6,000 to 7,900. The increase was attributed to an increase in production of granulocytes. No reason for the changes was proposed (Murphy et al., 1971).

Lithium is generally administered orally as lithium carbonate. It is absorbed very efficiently by the gastrointestinal tract, with peak serum concentration after a single dose of lithium being achieved in about 30 min. Lithium crosses cell boundaries at a relatively slow rate, achieving a distribution corresponding to that of total body water 5-6 days after. Lithium distribution may vary with the organ and from individual to individual. It appears to be relatively slow to cross the blood-brain barrier, although this too varies (Herrero, 1973). Lithium is excreted almost entirely in the urine, although small amounts may appear in the feces. Sixty to 70% of the filtered load is reabsorbed in the proximal renal tubule, where it competes with sodium in the renal transport mechanisms, leading to higher lithium retention in low-sodium situations (Singer and Rotenberg, 1973).

In treatment of acute affective disorders, lithium is given to raise serum levels to 2.0 mEq/l or until symptoms remit. Prophylactic lithium levels usually range between 0.6 and 1.5 mEq/l in the serum. The major hazard of lithium use is the slight difference between therapeutic and toxic levels. Side effects occurring occasionally at low doses and with serum levels below 2.0 mEq/l include mild abdominal distress, vomiting, polyurea, thirst, general muscle weakness, continuous fine tremor of the hands, general fatigue or lethargy, some dermatologic lesions, and goiter. Toxic signs occurring as serum levels rise to 2.0-3.0 mEq/l affect primarily the central nervous system and include lethargy, slurred speech, anorexia, vomiting, diarrhea, stupor, coma, convulsions, and coarse tremor. Increasing stupor, coma, and convulsions appear at levels above 3.0 mEq/l. Toxicity may occur through overdose, decreased sodium or water intake, or intercurrent illness (Tupin, 1970). Serum level monitoring is the usual procedure to assure the proper lithium levels and to prevent toxic effects, but many patients appear to be particularly sensitive to lithium, and cases where toxic effects and even permanent damage to the central nervous system have occurred at serum lithium levels below 2.0 mEq/l have been reported (Cohen and Cohen, 1974).

In face of the observed prophylactic action of lithium, it is interesting that a relationship has been reported between high lithium levels in drinking water and lower rates of admission to mental hospitals in Texas (Dawson et al., 1972). However, the true statistical significance of this report has been called into question (Pokorny et al., 1972), and the amounts of lithium actually consumed, estimated at 0.1 mg/day, are far below those prescribed in psychiatric use, approximately 900 mg/day.

## REFERENCES

Andreasen, N. J. T. Mechanism of lithium carbonate in manic-depressive illness. Dis. Nerv. Syst. 32(5):335-341, 1971.

Blachly, P. Lithium content of drinking water and ischemic heart disease. N. Engl. J. Med. 281:682, 1970.

Blando-Hoegler, C. F. A study of the effects of lithium chloride on embryonic and tissue specific isoenzyme patterns of Rana pipiens pipiens. Diss. Abstr. B 35(5):2036, 1974.

Boulos, B. M., B. Carnow, N. Naik, J. P. Bederka, R. F. Kauffman, and D. L. Azarnoff. Placental transfer of lithium and environmental toxicants and their effects in the new born. Fed. Proc. 32(3:1):745, 1973.

Cade, J. F. J. Lithium salts on the treatment of psychotic excitement. Med. J. Aust. 36:349, 1949.

Cohen, W. J., and N. H. Cohen. Lithium carbonate, haloperidol, and irreversible brain damage. J. Am. Med. Assoc. 230(a):1283-1287, 1974.

Dawson, E. B., T. D. Moore, and W. J. McGanity. Relationship of lithium metabolism to mental hospital admission and homicide. Dis. Nerv. Syst. 33(8): 546-556, 1972.

DeFeudis, F. V. Actions of lithium on cerebral carbohydrate metabolism. Res. Commun. Chem. Pathol. Pharmacol. 5(3):789-796, 1973.

denHertog, A., and E. J. Ploeger. Mechanism of action of lithium salts. Psychiatr. Neurol. Neurochir. 76(6):529-535, 1973.

Dutta, S. K., and A. Bhattacharyya. Lithium and its uses. Bangladesh Pharmacol. J. 3(4):5-12, 1973.

El-Sheikh, A. M., A. Ulrich, and T. C. Broyer. Effect of lithium on growth, salt absorption, and chemical composition of sugar beet plants. Agron. J. 65:755-758, 1971.

Englemann, W. Slowing down of circadian rhythms by lithium ions. Z. Naturforsch. 28(11-12):733-736, 1973.

Ezdakova, L. A. Effect of lithium top-dressing on photosynthesis and respiration in tobacco leaves. Nauchn. Dokl. Vyssh. Shk. Biol. Nauki 2:137-142, 1962.

Gilman, H., and J. J. Eisch. Lithium. Sci. Am. 208(1): 88-102, 1963.

Gralla, E. M., and H. M. McIlhenny. Studies in pregnant rats, rabbits, and monkeys with lithium carbonate. Toxicol. Appl. Pharmacol. 21(3):428-433, 1972.

Gustafson, T., and P. Lenicque. Mitochondria in the developing sea urchin egg. Exp. Cell Res. 3:251-274, 1952.

Herrero, F. A. Lithium carbonate toxicity. J. Am. Med. Assoc. 226(a):1109-1110, 1973.

Kabanov, V. V., and N. A. Myasoedov. Toxicity of alkali metal cations for tomato plants. Fiziol. Rast. 21(2):391-397, 1974.

Ketu, S. S. Norepinephrine in the central nervous system and its correlations with behavior. Brain and Human Behavior Symposium, 1972. p. 115-129.

King, R. C. Effects of alkali metals ions in development of drosophila, with special reference to lithium-induced abnormalities. Proc. Natl. Acad. Sci. U.S.A. 39(5):403-407, 1953.

Kirk-Othmer Encyclopedia of Chemical Technology. New York, John Wiley & Sons. 1967.

Leung, A. S. Lithium carbonate. Can. Psychiatr. Assoc. J. 15(2):189-199, 1970.

Mellerup, E. T., and O. J. Rafaelson. Heterogeneity and biomedical findings in manic-melancholic disorders. Acta Psychiatr. Scand. 50(1):104-111, 1974.

Merck Index, 8th ed. Rahway, N.J., Merck & Co., Inc. 1968.

Mineral Facts and Problems. U.S. Bureau of Mines. 1970.

Murphy, D. C., F. K. Goodwin, and W. E. Bunney. Leukocytosis during lithium treatment. Am. J. Psychiatry 127(11):1559-1561, 1971.

OPD Chemical Buyers Directory, 63rd ed. New York, Schnell Publishing Co., Inc. 1975.

Perez-Cruet, J. Stimulation of serotonin synthesis by lithium. J. Pharmacol. Exp. Ther. 178(2):325-330, 1971.

Pokorny, A. D., D. Sheehan, and J. Atkinson. Drinking water lithium and mental hospital admissions. Dis. Nerv. Syst. 33(10):649-659, 1972.

Polatin, P. Lithium carbonate prophylaxis in affective disorders: Clinical vs. research applications. Dis. Nerv. Syst. 7):472-475, 1972.

Polumbo, R. A., A. Branzi, J. S. Schroeder, and D. C. Harrison. The antiarrhythmatic effect of lithium chloride for experimental ouabain induced arrhythmias. Proc. Soc. Exp. Biol. Med. 142(4):1200-1204, 1973.

Registry of Toxic Effects of Chemical Substances. U.S. Department of Health, Education, and Welfare. 1975.

Schubert, J. Effect of chronic lithium treatment on monoamine metabolism in rat brain. Psychopharmacologia 32(3):301-311, 1973.

Sheard, M. H. Effect of lithium on human aggression. Nature 230(5289):113-114, 1971.

Shopsin, B. Effects of lithium on thyroid function. Dis. Nerv. Syst. 31(4):237-244, 1970.

Singer, I., and D. Rotenberg. Mechanisms of lithium action. N. Engl. J. Med. 289(5):254-260, 1973.

Szabo, K. T. Teratogenic effect of lithium carbonate in the foetal mouse. Nature 225:73-75, 1970.

Trieff, N. M., S. M. Frey, M. S. Rao, H. Bunce, and B. Herman. Analysis for lithium in Texas drinking waters. Tex. Rep. Biol. Med. 31(1):54-78, 1973.

Tupin, J. P. The use of lithium for manic-depressive psychoses. Hosp. Commun. Psychiatry 21(3):73-80, 1970.

Unpublished data from the University of Kentucky. Toxicity of metals to bass embryos. 1975.

Vizi, E. S., P. Illes, A. Ronai, and J. Knoll. Effect of lithium on acetylcholine release and synthesis. Neuropharmacology 11(4):521-530, 1972.

Voors, A. W. Does lithium depletion cause atherosclerotic heart-disease? Lancet 2:1337-1339, 1969.

Weinstein, M. R., and M. Goldfield. Cardiovascular malformations with lithium use during pregnancy. Am. J. Psychiatry 132(5):529-531, 1975.

# CHEMICAL HAZARD INFORMATION PROFILE

## Maleic Anhydride

Date of report: August 1, 1978

This chemical was chosen for study because of TSCA Section 8(e) submissions describing worker complaints following possible exposure to the chemical.

The following recommendations are made regarding further OTE evaluation of the possible health or environmental hazards of maleic anhydride:

(1) Check the results of the reported rat carcinogenicity study to determine if tumors were found at sites remote from the injection site--The presence of remote tumors indicates a greater potential for carcinogenic action.

(2) Check the status of maleic anhydride in OAQPS--They have conducted some investigations of the chemical.

(3) Transmit this report to NIOSH and OSHA--Most exposure to maleic anhydride apparently occurs in the workplace.

(4) Update this Chemical Hazard Information Profile based on the above.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

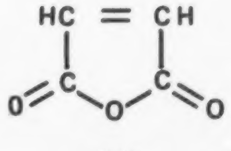
Any recommendations based on the report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

## Chemical Identity

Synonyms: Cis-butendioic anhydride, 2,5-furandione, toxilic anhydride

CAS No.: 108-31-6

The following diagram illustrates the chemical structure of maleic anhydride:



Maleic anhydride, $C_4H_2O_3$, is a white crystalline solid with an acrid odor. It melts at 52.8°C and boils at 202¼C. Maleic anhydride is soluble in water, acetone, hydrocarbons, ether, chloroform, and petroleum ether (ITII, 1976). It is also soluble in ethyl acetate and benzene (Patterson et al., 1976) and slightly soluble in carbon tetrachloride (Lowenheim and Moran, 1975). Maleic anhydride is combustible, with an ignition temperature of 476.67°C and flammable limits of 1.4-7.1% volume in air (ITII, 1976).

## Production and Use

Ninety-one percent of the total maleic anhydride produced in the United States is formed through oxidation of benzene, 6% through oxidation of n-butane, and 3% as a by-product of phthalic anhydride production. Benzene is oxidized in the vapor phase with a vanadium catalyst. Reaction gases include a maleic anhydride-maleic acid mixture, carbon dioxide, water, and some unreacted benzene (Lowenheim and Moran, 1975). n-Butane is also oxidized in the vapor phase. CEH suggests that a complex phosphorus vanadium catalyst is used, but no specific information is available (CEH, 1976).

Total production of maleic anhydride has increased at a 7.6% annual rate from 1969 to 1974. In 1974 production increased by only 2.8%, and in 1975 it decreased by 27% to 211 million lb. This decrease was caused by feedstock restraints and impact of the recession. Production rates from 1975-80 are expected to rise at an annual rate of 10%. In 1980, 16% production (as opposed to 6% in 1976) should be based on n-butanes (CEH, 1976).

CEH lists 10 U.S. production companies operating in 1976. Two, Amoco Chemicals and Ashland Chemical, were expected to begin operation late in the year. Production capacities of these companies were projected to be expandable to 90 million lb per year. Production of U.S. Steel was predicted to expand to 87 million lb per year (CEH, 1976).

The U.S. manufacturers of maleic anhydride are listed below for the year of 1976. U.S. capacity adds up to 485 million lb. This comprises 31% of the total world capacity (CEH, 1976).

| Manufacturer | Production capacity ($10^6$ lb/year) |
|---|---|
| Amoco Chemicals Corp., Joliet, Ill. | 60 |
| Ashland Chemicals Co., Neal, W. Va. | 60 |
| Koppers Co., Bridgeville, Pa., | 34 |
| Chicago, Ill. | 10 |
| Monsanto Industrial Chemicals Co., St. Louis, Mo. | 105 |
| Petro-Tek Chemicals Corp., Houston, Tex. | 50 |
| Reichhold Chemicals Corp., Elizabeth, N.J., | 30 |
| Morris, Ill. | 60 |
| Tenneco Chemicals Inc., Fords, N.J. | 26 |
| U.S. Steel Corp., Neville Island, Pa. | 50 |

All uses of maleic anhydride involve its application as a chemical intermediate. In 1975, 58% of the total maleic anhydride consumed in the U.S. was used in unsaturated polyester resins. Of these resins, 78% were used in reinforced plastic applications and 22% in nonreinforced plastics and resins. Four percent of the maleic anhydride consumed was used in the production of fumaric acid, 9% in agricultural chemicals (malathion, maleic hydrazide, and captan), and 3% in alkyd resins. Twenty-six % of maleic anhydride was used in miscellaneous applications such as lubricating additives, chlorendic anhydride and acids, copolymers, reactive plasticizers, malic acid, and surface-active agents (CEH, 1976; SRI, 1977).

## Health Aspects

Application of maleic anhydride consists only of use as a chemical intermediate, limiting exposure to occupational sources. The vapors and dust of maleic anhydride are acute irritants of eyes, skin, and upper respiratory tract. Maleic anhydride can be a sensitizer of the skin and respiratory tract (ACGIH, 1971).

Subacute inhalation of maleic anhydride can cause severe headaches, nosebleeds, nausea, and temporary impairment of vision. It can also lead to conjunctivitis and corneal erosion (Kirk-Othmer, 1968).

Patterson et al. (1976) state that repeated exposure to concentrations above 1.25 ppm has caused asthmatic responses in workers. Allergies have developed so that lower concentrations of maleic anhydride cannot be tolerated. An increased incidence of bronchitis and dermatitis has also been noted in workers with long-term exposure to maleic anhydride. One case of pulmonary edema in a worker was reported (Patterson et al., 1976).

In rats, maleic anhydride has an oral TDL of 850 mg/kg. Subcutaneous TDL is 610 mg/kg/61 weeks. Maleic anhydride is a carcinogen in rats administered subcutaneously. Other toxic effects are liver injury and histological changes (ITII, 1976).

Thome-beau et al. (1969) found that maleic anhydride strongly inhibits the enzyme ATP thiamine pyrophosphotransferase. This enzyme is a kinase which functions to catalyze the transfer of phosphate from ATP or, much more infrequently, from another nucleoside triphosphate to its substrate.

Obaid et al. (1972) treated human red cells with maleic anhydride. As a result of this treatment, potassium and sodium permeability increased, sodium to a lesser extent. Permeability of sulfate and chloride decreased to the same extent.

OSHA has set forth an 8-hr time weighted average of 0.25 ppm in the air. The TLV is likewise 0.25 ppm. It is stated, however, that further experience is needed to confirm or deny the suitability of this limit (ACGIH, 1971).

## Health Aspects of a Reaction Product, Benzene

Ninety-one percent of maleic anhydride produced in the U.S. is formed through oxidation of benzene. Reaction gases consist of benzene and maleic anhydride, among others (Lowenheim and Moran, 1975).

Benzene has various toxic effects. Chronic effects include anorexia, nausea, fatigue, weakness, dizziness, nervousness, and irritability. Acute symptoms include stimulation of the central nervous system, then depression, with death via respiratory paralysis. Also involved are respiratory irritation, pulmonary edema, and gastrointestinal irritation with vomiting and colic. Benzene is also a carcinogen (ITII, 1976).

The separate effects of maleic anhydride and benzene are fairly well documented. Data on the health aspects of exposure to a combination of the two as reaction products are nonexistent.

## Environmental Aspects

The largest quantity of maleic anhydride emitted (2.96 million lb per year) escapes as a result of phthalic anhydride production. Other sources of emission are maleic anhydride production (0.85 million lb), end product manufacture (0.85 million lb), and product handling and packaging losses (0.06 million lb). The total amount of maleic anhydride released from these sources is 4.72 million lb (Patterson et al., 1976).

Patterson et al. have made estimates of maximum average concentrations for 1 and 24 hr. The maximum 1-hr concentration is 0.20 ppm, and the maximum 24-hr concentration is 0.10 ppm (Patterson et al., 1976).

The primary method of emission control is to scrub the uncondensed portion of the reaction effluent after it passes through a partial condenser. Agaev et al. (1976) have found that maleic anhydride can be detoxified by oxidation with a 97-98% efficiency. Matsui et al. (1975) report that maleic anhydride in wastewater is easily decomposed by test-activated sludge. Developmental work is being done to control maleic anhydride emissions.

## REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). Documentation of Threshold Limit Values for Substances in Workroom Air, 3rd ed. 1971. p. 263.

Agaev, A. S. et al. Detoxification of phthalic anhydride industry discharges. Khim. Tekhnol. Topl. Masel 11:44-45, 1976. (English abstract)

Chemical Economics Handbook (CEH). Maleic Anhydride. Menlo Park, Calif., Stanford Research Institute. July 1976.

ITII (International Technical Information Institute). Toxic and Hazardous Industrial Chemicals Safety Manual. Tokyo. 1976.

Kirk-Othmer Encyclopedia of Chemical Technology, 2nd ed., vol. 12. New York, John Wiley & Sons. 1978.

Lowenheim, Frederick A., and Marguerite K. Moran. Industrial Chemicals, 4th ed. New York, John Wiley & Sons. 1975. p. 514-518.

Matsui, S. et al. Activated sludge degradability of organic substances in the waste water of the Kashima petroleum and petro chemical industrial complex in Japan. Prog. Water Technol. 7:645-659, 1975.

NIOSH. Registry of Toxic Effects of Chemical Substances. 1975.

Obaid, A. L. et al. Effects of maleic anhydride on the ionic permeability of red cells. J. Membr. Biol. 9:385-401, 1972.

Patterson, R. M, et al. Assessment of maleic anhydride as a potential air pollution problem. U.S. NTIS, PB Report, Issue PB-258363, 1976.

SRI (Stanford Research Institute). A Study of Industrial Data on Candidate Chemicals for Testing. Menlo Park, Calif. August 1977.

Thome-beau, F. et al. ATP thiamine pyrophosphotransferase. Purification and reaction. Biochim. Biophys. Acta 185:11-21, 1969.

# CHEMICAL HAZARD INFORMATION PROFILE

## Methanol

Date of report: July 11, 1977

This chemical was chosen for study because of projected trends in production and use patterns.

It is recommended that a more comprehensive literature search be performed on methanol. The CHIP report will then be revised and the review process repeated.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

### Chemical Identity

Methanol or methyl alcohol, CH3OH, is a colorless neutral liquid at ambient temperature with a mild odor. It has a boiling point of 65°C and is infinitely soluble in water, alcohol, and ether. By far the largest use of methanol is in the production of formaldehyde (CEH, 1976).

### Production and Use

At present, the most important method of methanol manufacture is by a high-pressure process involving a pressurized synthesis gas (usually made by the re-forming of straight natural gas and consisting of a mixture of CO, $CO_2$, and $H_2$) which is converted into methanol according to the following reactions:

$$CO + 2H_2 \qquad CH_3OH$$

$$CO_2 + 3H_2 \qquad CH_3OH + H_2O$$

Essentially all methanol manufactured in the U. S. is based on natural gas. In a typical high-pressure process, the synthesis gas is desulfurized, cooled to remove steam, compressed to 4,300 psi, mixed with recycled gas, and passed to the converter. The conversion to methanol takes place at temperatures around 300°C in the presence of a zinc-chromium catalyst. The methanol-containing gases are then cooled, condensed, and purified by distillation. Methanol of 99+% purity and an overall yield of 60% from natural gas may be obtained by these high-pressure processes. The low-pressure processes are responsible for the balance of domestic synthetic methanol production (roughly 30-40%). This method operates at pressures around 750 psi and at temperatures near 250°C. There are various other differences between high- and low-pressure processes, with the end result being a purer crude methanol, greater production efficiency, and lower operating costs for the low-pressure process. See Tables 1 and 2 for domestic production figures and a listing of producers. Several companies have developed medium-pressure processes; however, no domestic plants are currently using this method. Various other processes contribute small amounts of methanol to overall domestic production, although none are presently of great significance.

The largest end use for methanol is in the production of formaldehyde. Other large-volume chemicals based on methanol include dimethyl terephthalate, methyl halides, methylamines, methyl methacrylate, and various solvent uses, among others. See Table 3 for a more complete breakdown of the methanol consumption figures.

Methanol was in tight supply at points in 1973-74. However, the recession has cut demand, and the supply has been adequate from 1975 to the present. Methanol may become scarce again when the building industry picks up and demand for formaldehyde resins increases. New plants, slated to come on stream in 1979 and 1980, will relieve the shortfall.

The price of methanol has increased significantly since 1973 and is expected to continue upward (CEH, 1974).

## New Developments

Methanol from Coal. The growing scarcity of natural gas in the United States has resulted in an increased interest in producing methanol from coal. Several companies have studies coal gasification units which utilize a variety of methods. A number of these proposed methods are currently being tested in pilot plants. In most processes, coal is fed to a gasifier, where the raw material reacts with steam to produce hydrogen gas and carbon monoxide. The raw gas is then processed to remove sulfur. The clean synthesis gas is subsequently used to produce methanol.

Table 1. Annual Domestic Methanol Production ($10^6$ lb)

| Year | Natural | Synthetic | Total |
|---|---|---|---|
| 1960 | 14.3 | 1,965.9 | 1,980.2 |
| 1965 | 8.8 | 2,868.6 | 2,877.4 |
| 1970 | 10[a] | 4,931.7 | 4,931.7 |
| 1975 | 10[a] | 5,176.3 | 5,176.3 |

[a] Source: CEH, 1976. Approximation.

Table 2. Domestic Producers of Methanol and 1974 Capacity

| Producer/location | Capacity ($10^6$ lb) |
|---|---|
| Air Products and Chemicals, Inc. | |
| Pensacola, Fla. | 332 |
| Borden Chemical | |
| Geismar, La. | 1,061 |
| Celanese Corp. | |
| Bishop, Tex. | 398 |
| Clear Lake, Tex. | 1,525 |
| Commercial Solvents Corp. | |
| Sterlington, La. | 332 |
| E. I. du Pont de Nemours & Co. | |
| Beaumont, Tex. | 1,326 |
| Orange, Tex. | 762 |
| Georgia-Pacific Corp. | |
| Plaquemine, La. | 663 |
| Hercules, Inc. | |
| Plaquemine, La. | 663 |
| Monsanto Co. | |
| Texas City, Tex. | 663 |
| Rohm and Haas Co. | |
| Deer Park, Tex. | 146 |
| Tenneco Inc. | |
| Houston, Tex. | 530 |

Source: CEH, 1974.

Table 3. Domestic Consumption of Methanol (%)

| | 1968 | 1973 |
|---|---|---|
| Formaldehye | 44.7 | 39.0 |
| Solvent usage[a] | 9.9 | 7.9 |
| Dimethyl terephthalate | 5.5 | 6.1 |
| Methyl halides | 5.4 | 6.1 |
| Methylamines | 4.2 | 3.3 |
| Methyl methacrylate | 4.1 | 3.7 |
| Acetic acid | 0.2 | 3.4 |
| Glycol methyl ethers[b] | 1.9 | 1.1 |
| Inhibitor for formaldehyde[c] | 1.2 | 0.9 |
| Exports[d] | 1.9 | 11.6 |
| Miscellaneous[e] | 20.9 | 16.9 |

Source: CEH, 1974.

[a] Methanol is used as a solvent for many substances including: dyes; nitrocellulose and ethyl cellulose; polyvinyl acetate; butyral shellac and modified resin; others.

[b] The single largest use for ethylene glycol monomethyl ether is as a deicing agent in jet fuels; it also finds use as a solvent for protective coatings (mainly lacquer formulations) and in textile dyeing processes. Ethylene glycol monomethyl ether is also used as an intermediate for di(2-methoxyethyl)phthalate plasticizer production.

[c] Formaldehyde has a tendency to polymerize on storage, so methanol is sometimes added (about 0.03 lb of methanol per lb of 37% formaldehyde) to inhibit polymerization.

[d] 1966-68 were light years for the export of methanol; no explanation was offered.

[e] Methanol is used in the production of numerous other chemicals (e.g., methyl acetate, dimethylaniline, methyl acrylate, o-nitroanisole, sodium methylate, polyphenylene oxide, and dimethyl phthalate), though none represents a significant end use for methanol by itself. Very little methanol is currently used as an antifreeze in automobile engines because of the high operating temperatures of modern engines. An estimated 50 million lb of methanol was used in 1970 as a deicer in gasoline, and this market is expected to grow moderately. Seventy-five million lb of methanol was used in 1969 as an antidetonant injection fluid in aircraft fuel; this use of methanol, however, is being phased out for unknown reasons.

To date, no plants have been built in the United States for this purpose. However, a West German commercial gasification operation is slated to come on stream in 1978. An unnamed industry source believes that the first large, domestic coal-based methanol unit will not come much before 1982. However, if this initial plant proves successful, others are likely to follow.

The major difficulties to be overcome are those associated with gas cleanup and the various engineering design problems involved with the incorporation of a methanol synthesis unit in a gasification plant. A coal conversion plant would most likely be based on lignite or bituminous coal (CEH, 1976).

Sewage Treatment Applications. A potentially large use for methanol is as a carbon source for bacteria to aid in the (anaerobic) conversion of nitrates to nitrogen gas and carbon dioxide gas. Methanol is regarded as the most appropriate source of carbon for denitrification in an activated sludge or trickling filter installation because of its low cost and miscibility with water. Washington, D.C., was scheduled to begin using methanol for this purpose in 1975; if the project succeeds, other communities are expected to follow the Washington lead. Estimates for this market are 30 million gallons in 1979 and 392 million gallons by 1985 (CEH, 1976).

Production of Animal Feed. Another use for methanol may be as a substrate for the fermentation production of animal feed protein (single-cell protein). A domestic pilot plant is in operation at Bartlesville, Okla.; however, the use of single-cell protein is on a small scale in the United States because of low soybean prices, a restricted market, and resistance to its use by humans. This market is not expected to become significant in the United States during the next 5 years (CEH, 1976).

Mega-Methanol Plants and Liquid Chemical Fuel. During the past several years, considerable worldwide interest has been stimulated in the manufacture of massive quantities of methanol for use as a direct fuel or as a feed for conversion to substitute natural gas (SNG). The original intention was to divert currently flared Middle East natural gas to liquid chemical fuel (an impure form of methanol) production. The methanol thus produced would be shipped to the United States for use directly as a fuel or for regasification to SNG. Several projects were started in 1973 but were subsequently cut back or phased out.

The impetus for construction of mega-methanol plants comes from the potential cost savings obtained from the long-distance shipping of liquid chemical fuel (LCF) as opposed to liquefied natural gas (LNG). Despite higher production costs for LCF, methanol is far cheaper to ship because it can be carried in conventional crude oil tankers. LNG, on the other hand, must be shipped in expensive cryogenic tankers. Following delivery, LCF is also cheaper to store. Nevertheless, very large methanol-producing plants would be needed to make LCF production economically feasible. Without a large capacity, it is doubtful that a plant could keep a fleet of tankers operating steadily and economically. The break-even mileage beyond which LCF is more economical to ship than LNG is debatable. Industry estimates range from a low of 1,800 miles to as high as 5,000-6,000 miles.

Methanol fuel plants were formerly seen for locations with abundant cheap natural gas. The Arab oil embargo, however, has shifted interest to domestic coal-based facilities. Construction of mega-methanol plants has been held up for two reasons: coal-based technology has not been tested out on a commercial scale, and a tremendous amount of capital is required to build such a plant. One estimate places the investment at $1 billion for the first 10,000-tons-per-day methanol plant. The uncertainty of performance and the possibility of failure combine to restrain investors. Nevertheless, forecasted demand for all nonchemical uses of methanol indicates that the demand by 1990 could equal the production from several mega-methanol plants (CEH, 1976).

Use as a Motor Fuel. In 1968, an estimated 66 million lb (10 million gal) of methanol was used as a fuel (in modified, predominantly racing engines) and as a fuel additive (e.g., for increased thrust in turbine engines). These end uses were expected to increase to 100 million lb (15 million gal) by 1973. Although methanol use as a fuel in special situations was expected to continue upward, it was not seen as a large market because methanol tends to clean out rust in storage tanks and piping resulting in contaminated fuel. During the gasoline shortage of a few years back, however, interest in using methanol as an automobile fuel or fuel extender was renewed. The situation at that time made the issue of fuel availability more important than the greater production costs of methanol.

Although methanol can be used directly as an automobile fuel, it is more likely in the near term to find use in fuel blends. Use of methanol as a fuel extender obviates the need for engine and other modifications necessary in a conversion of cars from gasoline to liquid chemical fuel (design changes are possible in new cars, but to retrofit old cars is costly). Several test cars have been successfully operated on methanol or methanol/gasoline mixtures. The advantages of blends are reduced emissions and improved octane rating; the disadvantage is engine stalling resulting from phase separation following moisture pickup. Although this can be solved technically, it would result in higher fuel distribution and handling costs. Other problems (vapor lock, hard cold-weather starting, corrosion problems, incompatibility with plastics, etc.) can also be solved with the proper modifications, or so the proponents of fuel blends claim.

Some quarters (e.g., the American Petroleum Institute) feel that straight methanol is preferable to the use of blends with gasoline for automobiles. Liquid chemical fuel and high methanol blends are cleaner burning, have greater fuel efficiency (usable at higher compression ratio than gasoline), and are not susceptible to phase separation. Nevertheless, because of supply problems and the inability of cars built for methanol to run on gasoline, straight methanol is foreseen only for use in taxis, municipal cars, or fleet operations in the near term.

During the next 5 years, consumption of methanol for automobile fuel applications is expected to remain small. One estimate places worldwide use of methanol for this purpose at 11 to 176 billion lb by 1985; another estimate is less optimistic and predicts that worldwide automotive fuel demand in 1985 will be 23 billion lb.

Methanol can also be used to produce methyl tertiary butyl ether (MTBE), an octane improver. Although there is competition from other materials, it has been estimated that at least 2.9 billion lb of methanol could be used for worldwide MTBE production in 1985 (CEH, 1976).

Gasoline from Methanol. Industry is developing a process for producing octane gasoline from methanol by examining the possibility of coupling the new technology with existing methanol processes to provide a new gasoline source from coal. The two-stage process has an anticipated yield of 90% (75-80% high-quality gasoline and the balance in less desirable, though usable, hydrocarbons). Another process attempts to convert coal to ethylene and produce substantial quantities of gasoline as a by-product. A demonstration plant using this process is under construction and, if it proves successful, offers the possibility of making either ethylene or gasoline as demand warrants. During the next 5 years, methanol demand for ethylene-gasoline production is expected to remain small. Nevertheless, some in industry feel that, in the long term, this process will offer tremendous opportunities for gasoline production (CEH, 1976).

Power Generation. One of the potentially largest new markets for methanol is power generation in peak loading gas turbines. Projected domestic methanol demand for this purpose is forecast at 29 billion lb by 1985. The basis for the optimistic projection is the foreseen increasing demand for gasified coal as a fuel. A coal gasification plant is very capital intensive; to ensure maximal utilization, the proposal is to use synthesis gas as fuel for power generation at times of peak demand and divert some of the gas to methanol production during off-peak hours. The stored methanol could be used to cover fuel shortages during peak electricity demand periods. Presently, there is not enough methanol available to operate a gas turbine in this manner, and until the mega-methanol plants (likely coal based) are built, this methanol market will not develop (CEH, 1976).

In Coal Slurry Pipelines. An Alaskan proposal suggests the use of methanol in lieu of water as the basis for a coal slurry which would be transported to southern California by tanker. The proposal is of interest in the western regions of the country also. There are a number of pluses to this idea: it would help alleviate concerns about the large volume of water diverted from agriculture to such large-scale industrial ventures; it is claimed that methanol can carry 75-80% coal, compared to 50% for water; and the pipeline could run economically at only 25-30% capacity. This concept also awaits the development of mega-methanol plants and is not expected to be significant before 1981 (CEH, 1976).

Miscellaneous. Methanol could conceivably be used in substantial quantities by the steel industry, either as a source of synthesis gas or of pure hydrogen. The ease of transport of methanol is the big plus in this potential market. Industry estimates vary from no substantial use of methanol in blast furnaces by 1985 to 75 to 95 million metric tons of methanol consumed worldwide by the same date for this purpose.

Another possible market is as a feedstock for reducing gas generation. Methanol could be used as a precursor of hydrogen or synthesis gas, especially for the direct reduction of iron ore. Estimated methanol consumption in this area could account for 9 to 12.5 million metric tons per year worldwide by 1985.

Methanol has also been suggested as an alternate starting material for the synthesis of ammonia (CEH, 1976).

## Health Aspects

### Human

The toxic effects of methanol exposure are generally the same following both acute and chronic exposure. The underlying basis for this is the slow metabolic breakdown and removal of methanol and its by-products from the body such that a chronic response appears to be the result of a cumulative increase in these substances. Most instances of acute lethality follow the oral ingestion of methanol. Nevertheless, the symptomatologies of oral and inhalation exposure appear to be identical, though often less severe for the respiratory route.

Methyl alcohol is readily absorbed from both the gastrointestinal and respiratory tracts. The lethal dose in man lies between 2 and 8 oz, implying a high variation in individual susceptibility.

Mild and transient inebriation followed by drowsiness are immediate effects of methanol ingestion. This phase is followed by a symptom-free period of 6 to 30 hr, after which characteristic signs and symptoms of methanol poisoning develop: nausea, epigastric pain, vomiting, headache, narcosis, dizziness, delirium, blindness, acidosis, and acetonuria, among others (Treon, 1963; Gleason et al., 1969).

Acidosis appears to be the triggering mechanism for most symptoms of methanol poisoning regardless of route. Acidosis results from the metabolic oxidation of methanol to formic acid and also because of the unexplained tendency of other organic acids (e.g., lactic acid) to accumulate in the body. The severity of the response to methanol is said to be related to the intensity of this delayed acidosis.

Visual disturbances are the most distinctive aspect of methanol poisoning in man (Gleason et al., 1969). The effect on the eyes is attributed to optic neuritis, which characteristically subsides only to be followed by degeneration of the optic nerve, often leading to permanent blindness (Sax, 1968). It is generally agreed that metabolically formed formaldehyde is responsible for the ocular difficulties (Gleason et al., 1969).

A concentration of 2,000 ppm is barely detectable by odor and not irritating to man. Instances of fatal respiratory exposure are rare, but include a woman exposed to a calculated 4,000 to 13,000 ppm for 12 hr and a man exposed to 40,000 ppm for part of a working day. On the basis of human exposure, it was calculated that repeated 8-hr exposures to 3,000 ppm of methanol will lead to increasing concentrations of the alcohol and its toxic metabolites within the body due to the slow rate of excretion.

Skin absorption of the liquid and vapor can occur, but is not likely to lead to toxic effects. An estimated 1 oz of methanol must be absorbed through the skin to affect man (Patterson et al., 1975).

Human pathology studies of methanol fatalities (oral) have revealed damage to the gastrointestinal tract, lungs, liver, pancreas, spleen, and neurons of the brain (Treon, 1963).

## Laboratory Animals

Death in animals (nonprimates) following exposure to methanol is not due to acidosis, but to narcotic effects exerted on the central nervous system. Lab animals apparently have a greater alkaline reserve with which to combat acidosis than does man. Nevertheless, the susceptibility of animals to methanol varies with species and even among individuals of the same species.

Exposure to acute concentrations will generally produce the following responses in animals: increased breathing rate, nervous depression followed by excitation, irritation of mucous membranes, ataxia, partial paralysis, narcosis, convulsions, weight loss, and death due to respiratory failure. Necropsies have revealed considerable central nervous system degeneration (Treon, 1963).

### Hygienic Standards

Methanol's international hygienic standards are as follows: United States, West Germany, and Sweden, 260 mg/m$^3$ (8-hr TWA); East Germany and Czechoslovakia, 100 mg/m$^3$ (8-hr TWA); U.S.S.R., 5 mg/m$^3$ (acceptable ceiling concentration) (Winell, 1975).

## Environmental Aspects

### Losses

Emissions of methanol from solvent usage represent the largest category of losses to the environment. These sources, however, tend to be small and geographically scattered. Production emissions represent only a small portion of total methanol release. Nevertheless, because the losses tend to be heavily localized and not disperse as in the case for solvents, this source could represent a problem.

MITRE Corp. (1976) and Patterson et al. (1975) estimate the annual environmental loss of methanol at approximately 18% of total production. Thus, the Patterson et al. figure for 1974 is 1,242 million lb, while the MITRE value for 1975 (which suffered a 1.6 billion lb production decline) is 988 million lb. As noted previously, the largest loss category is solvents, which represent approximately 90% of all methanol losses. Production, handling, and end product manufacture represent the remaining 10%. See Table 4 for a listing of sources and their estimated emissions.

Table 4. Methanol Source and Emission Estimates (based on production of 6.7 billion lb)

| Source | Emissions[a] (10$^6$ lb/year) |
|---|---|
| Miscellaneous solvent usage | 575 |
| Industrial solvent usage | 538 |
| Methanol production | 68 |
| End product manufacture | 49 |
| Storage and handling | 12 |
| Total | 1,242 |

[a]Source: Adapted from Patterson et al., 1975
Based on 100% loss of solvents and 1% loss during production of methanol and end products.

The proposed mega-methanol plants may represent an appreciable hazard, especially if they tend to be clustered. If the 1% loss figure is accurate, the emissions from a single 10,000-metric-ton-per-day mega-methanol facility would be over 800 million lb per year. Couple with this the losses expected from the other proposed uses, especially as an auto fuel, and the increase in total emissions arising solely from the expected growth in present-day uses of methanol, and one can appreciate methanol's potential for causing future health and environmental problems.

### Atmospheric Chemistry

Methanol is not a significant component of photochemical smog, nor is it very active in the formation of photochemical products following irradiation (Patterson et al., 1975). Methanol, however, is reactive with oxidizing material in the atmosphere (MITRE Corp., 1976). Because of methanol's water solubility, rain would be expected to remove some from the air.

### Effects on Vegetation

Methanol has not been implicated in vegetation damage as have various other pollutants. However, a recent Russian study (reference unknown) has indicated that plants may be sensitive to methanol vapor. Concentrations above 0.2 mg/m$^3$ (0.15 ppm) produced a decrease in photosynthesis in several different tree species. This finding may be significant because it seems to indicate that plants are more sensitive to lower concentrations of methanol vapor than are either man or animals (Patterson et al., 1975).

### Effects on Inanimate Objects

Methanol as a solvent will attack some types of plastics, coatings, and rubbers (Patterson et al., 1975).

## REFERENCES

Chemical Economics Handbook (CEH). Menlo Park, Calif., Stanford Research Institute. 1974, 1976.

Gleason, Marion et al. Clinical Toxicology of Commercial Products, 3rd ed. Baltimore, The Williams and Wilkins Co. 1969.

MITRE Corp. Scoring of Organic Air Pollutants. Chemistry, Production and Toxicity of Selected Organic Chemicals. (For U.S. Environmental Protection Agency) 1976.*

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*This document was prepared for the U.S. Environmental Protection Agency by the MITRE Corp. It is a secondary source and does not cite its primary references. Thus, verification of some information is not possible. The environmental release data were taken from the NSF/Rann Research Program on Hazard Priority Ranking of Manufactured Chemicals.

Patterson, Robert M. et al. Assessment of Methyl Alcohol as a Potential Air Pollution Problem, vol. II. U.S. Environmental Protection Agency. 1975.

Sax, N. Irving (ed.). Dangerous Properties of Industrial Materials. New York, Van Nostrand Reinhold Co. 1968.

Treon, Joseph F. In Frank A. Patty (ed.), Industrial Hygiene and Toxicology, vol. II. New York, Interscience Publishers. 1963. p. 1409-1422.

Winell, Margareta. An international comparison of hygienic standards for chemicals in the work environment. Ambio 4:34-6, 1975.

# CHEMICAL HAZARD INFORMATION PROFILE

## Methylamines

Date of report: May 1, 1978

These chemicals were chosen for study because of their potential for being nitrosated and thereby forming nitrosamines. Certain nitrosamines are known carcinogens.

The following recommendations are made regarding further OTE evaluation of the possible health or environmental hazards of methylamines:

(1) Refer to OSHA--Most exposure to methylamines is confined to the workplace. There is a reported incident of fishermen fainting due to excessive concentrations of trimethylamine.

(2) Check on DOT status--Determine the potential for accidental spillage.

(3) Refer to OAQPS--Amines may be released into the air from manufacturing sites.

(4) Require Section 8(a) submissions--Determine the presence of methylamines in consumer products and revise this Chemical Hazard Information Profile accordingly.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

## Chemical Identity

All the methylamines are gaseous under normal temperatures and pressures. They have an ammonia-like odor, are quite basic, and are soluble in water and lower alcohols. Their salts are often used because they are solids of low volatility and thus more easily handled (Harwood, 1971). Respective $pK_a$ and boiling point (°C) values for the methylamines are monomethylamine, 10.64, -65; dimethylamine, 10.61, 7.4; and trimethylamine, 10.71 and 3.5 (Sutton, 1963).

## Production and Use

The methylamines are produced by reacting ammonia and methanol over a dehydrating catalyst. In 1973 the total domestic methylamine production capacity was 243 million lb. In 1975, 37 million lb of dimethylamine and 14 million lb of trimethylamine were sold. A significant portion of the methylamines produced are used captively as intermediates and are not sold (U.S. ITC, 1975). Production data from 1977 are as follows: Monomethylamine 60 million lb; Dimethylamine 100 million lb; and Trimethylamine 60 million lb (U.S. EPA (1979)).*

All the methylamines are used primarily as intermediates for chemicals used in medicine, pesticides, rubber vulcanization, and leather processing.

Some examples of compounds synthesized from methylamines follow. Monomethylamine is a starting material for N-oleyltaurine, a surfactant, and p-N-methylaminophenolsulfate, a photographic developer. It has possible uses in solvent extraction systems in the separation of aromatics from aliphatic hydrocarbons.

About half the dimethylamine produced is used to make dimethylformamide and dimethylacetamide, spinning solvents for acrylic fibers. Dimethylamine is also used in the manufacture of laurylmethylamine, a surfactant, thiuram derivatives, which are used as rubber accelerators, and 1,1-dimethylhydrazine, used as a rocket fuel. Its sulfate salt is used in leather processing to dehair hides.

Trimethylamine is used as a raw material in the production of choline, a poultry feed additive, and as a polymerization catalyst (Harwood, 1971; SRI, 1979).

Figures 1, 2, and 3 indicate additional general uses and potential exposure to methylamines. MITRE Corp. (1976) calculated that 20.6 million lb each of DMA and TMA are released annually to the environment.

## Health Aspects

### Acute Effects

In humans, methylamines are irritating to the lungs, eyes, and upper respiratory tract at concentrations of 20-100 ppm (Sutton, 1963). These compounds have a pungent ammoniacal odor; human olfactory thresholds are well below levels which produce irritation.

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*This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitation contained in the Inventory Reporting Regulations (40 CFR 710).

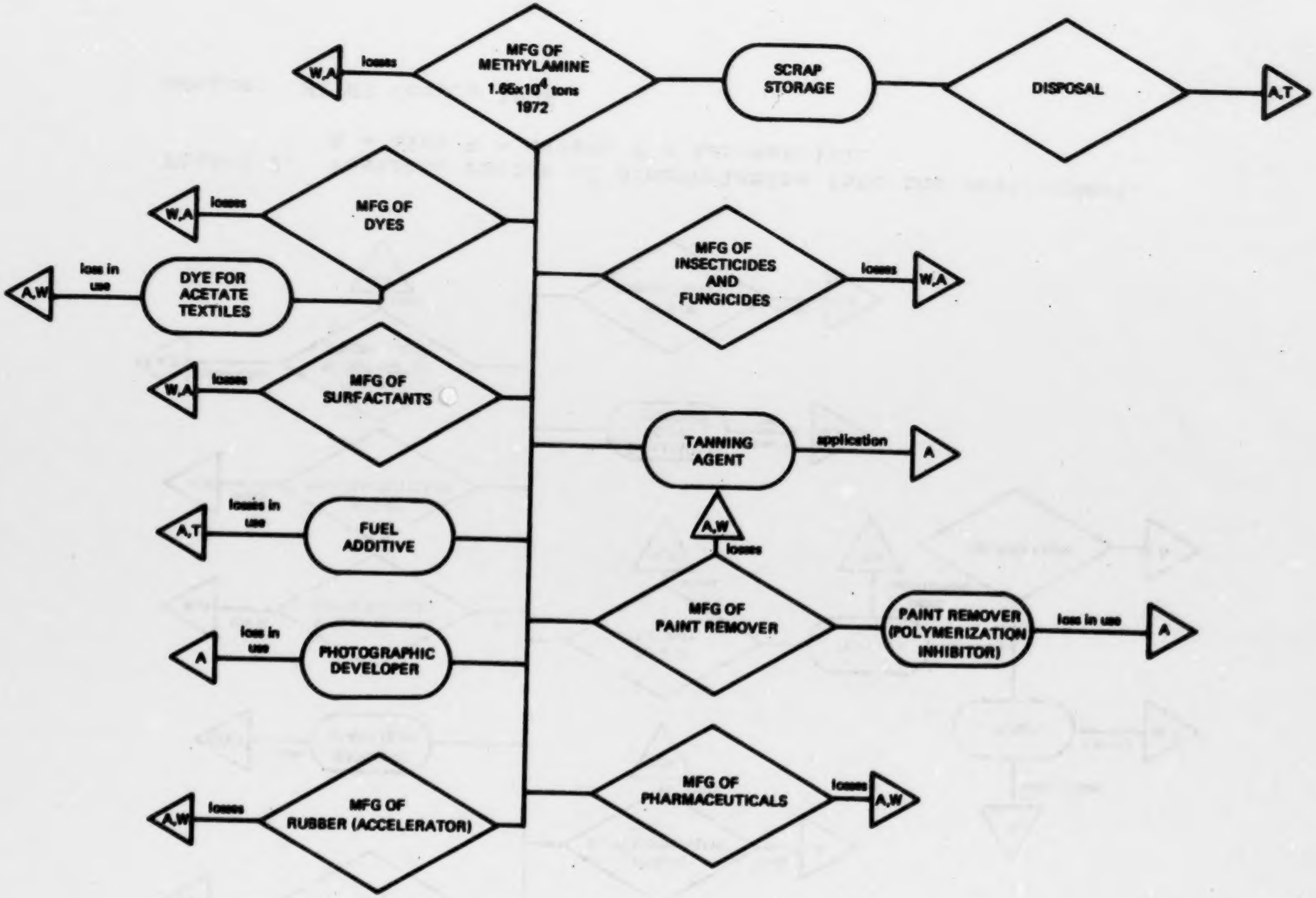
losses
W,A
MFG OF
METHYLAMINE
1.65x10^4 tons
1972
SCRAP
STORAGE
DISPOSAL
A,T
losses
W,A
MFG OF
DYES
loss in
use
A,W
DYE FOR
ACETATE
TEXTILES
MFG OF
INSECTICIDES
AND
FUNGICIDES
losses
W,A
losses
W,A
MFG OF
SURFACTANTS
TANNING
AGENT
application
A
losses in
use
A,T
FUEL
ADDITIVE
A,W
losses
MFG OF
PAINT REMOVER
PAINT REMOVER
(POLYMERIZATION
INHIBITOR)
loss in use
A
loss in
use
A
PHOTOGRAPHIC
DEVELOPER
losses
A,W
MFG OF
RUBBER (ACCELERATOR)
MFG OF
PHARMACEUTICALS
losses
A,W

Figure 1. Possible routes of methylamine into the environment. A = air; W = water; T= terrestrial.

Source: MITRE Corp., 1976.

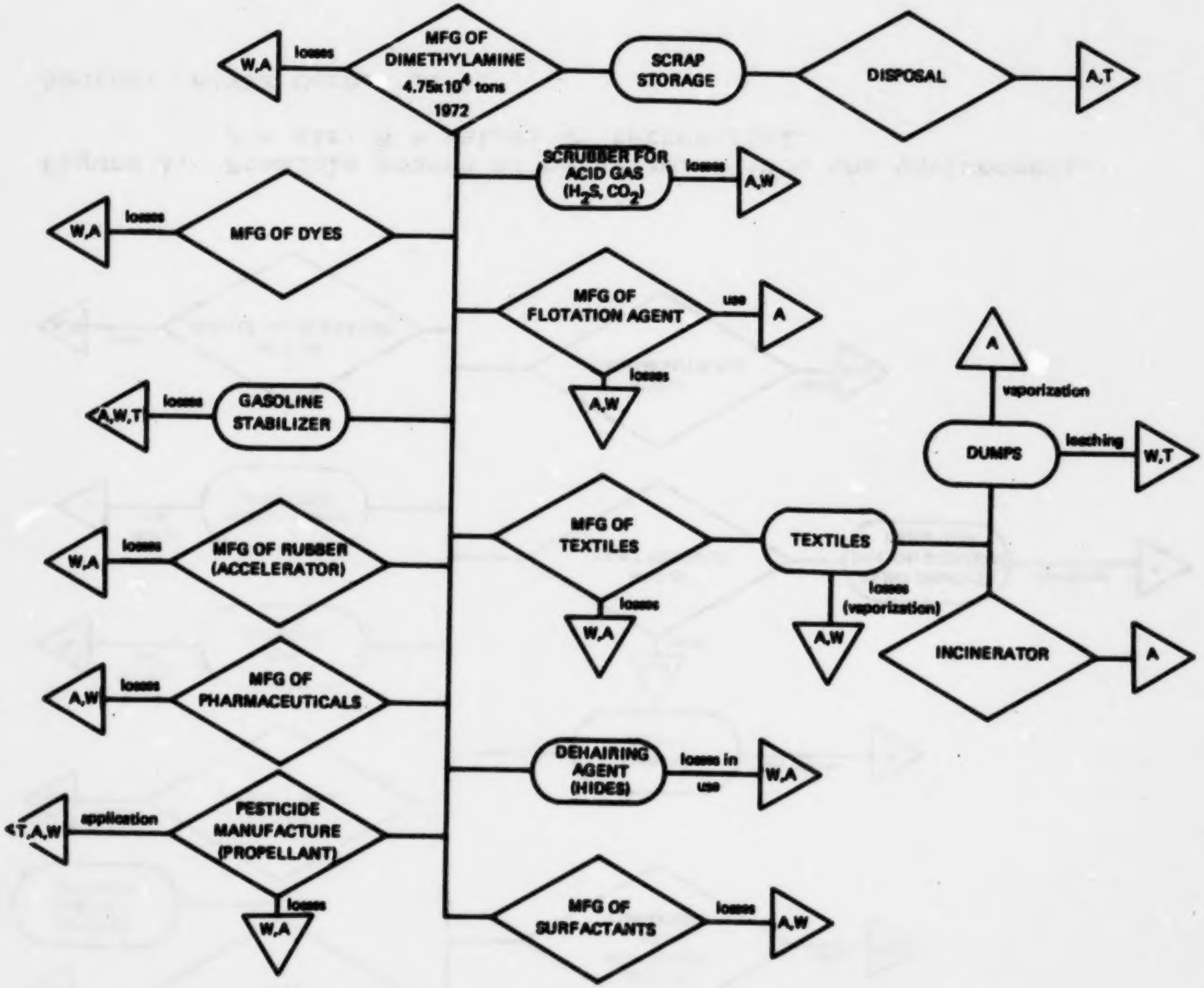
MFG OF DIMETHYLAMINE 4.75x10^4 tons 1972
losses
W,A
SCRAP STORAGE
DISPOSAL
A,T
SCRUBBER FOR ACID GAS (H2S, CO2)
losses
A,W
MFG OF DYES
losses
W,A
MFG OF FLOTATION AGENT
use
A
losses
A,W
GASOLINE STABILIZER
losses
A,W,T
MFG OF TEXTILES
losses
W,A
TEXTILES
losses (vaporization)
A,W
DUMPS
vaporization
A
leaching
W,T
INCINERATOR
A
MFG OF RUBBER (ACCELERATOR)
losses
W,A
MFG OF PHARMACEUTICALS
losses
A,W
DEHAIRING AGENT (HIDES)
losses in use
W,A
PESTICIDE MANUFACTURE (PROPELLANT)
application
T,A,W
losses
W,A
MFG OF SURFACTANTS
losses
A,W

Figure 2. Possible routes of dimethylamine into the environment. A = air; W = water; T = terrestrial.

Source: MITRE Corp., 1976.

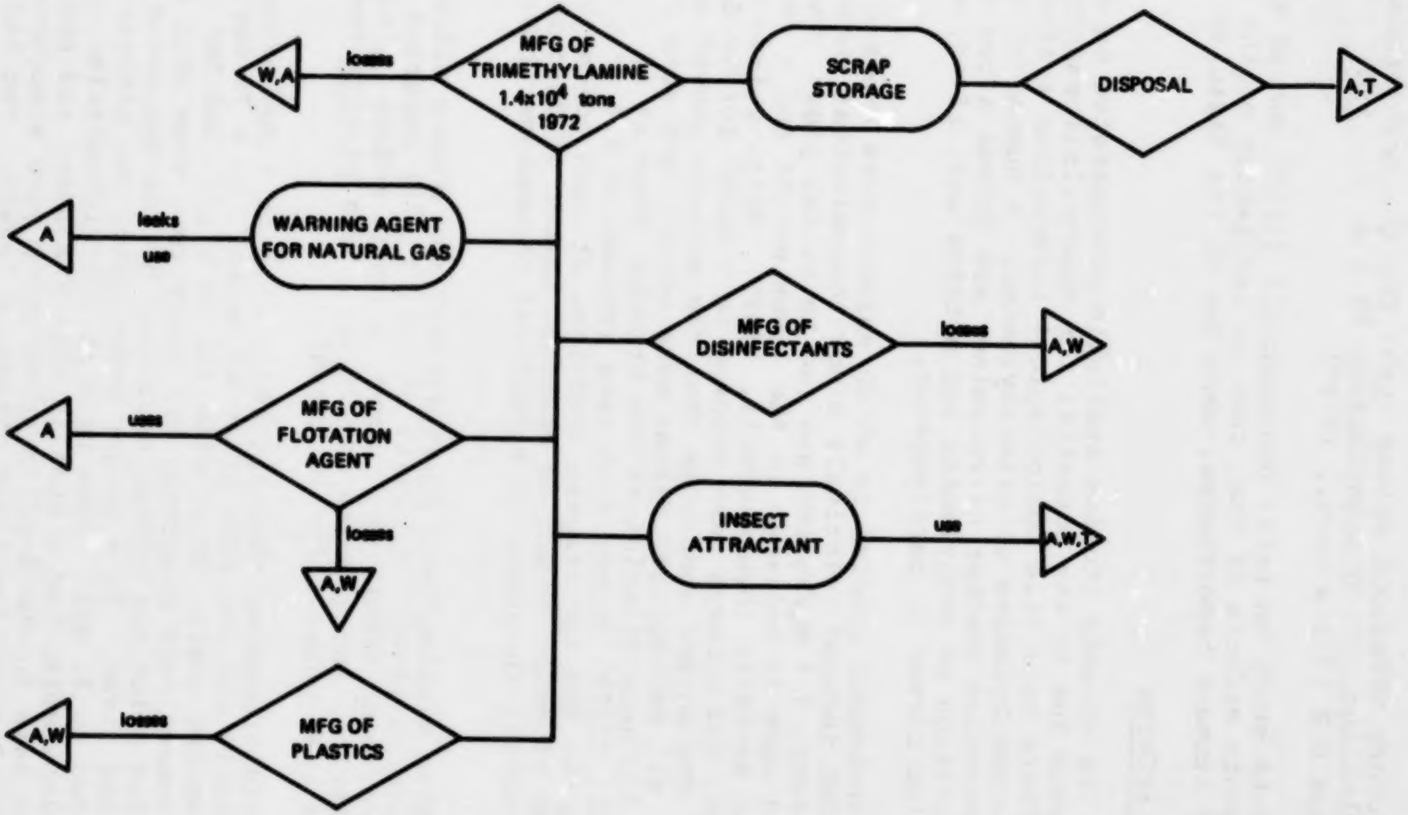
W,A
losses
MFG OF TRIMETHYLAMINE 1.4x10$^4$ tons 1972
SCRAP STORAGE
DISPOSAL
A,T
A
leaks
use
WARNING AGENT FOR NATURAL GAS
MFG OF DISINFECTANTS
losses
A,W
A
uses
MFG OF FLOTATION AGENT
losses
A,W
INSECT ATTRACTANT
use
A,W,T
A,W
losses
MFG OF PLASTICS

Figure 3. Possible routes of triethylamine into the environment. A = air; W = water; T = terrestrial.

Source: MITRE Corp., 1976.

The olfactory threshold values (ppb) for the methylamines are monomethylamines, 2D; dimethylamines 23.2 or 47; and trimethylamines 0.2 (Mitre Corp., 1976[a]).

In an acute study on rats, Dzhanashvili (1967) showed that some of the acute effects of DMA, such as irritation of the mucous membranes and stomach hemorrhages, were due to its basicity.

### Chronic Effects

Most of the chronic studies available concentrated on dimethylamine, largely due to the potential for dimethylnitrosamine formation. There is little toxicological information available concerning monomethylamine or trimethylamine. A number of studies attempt to determine whether nitrosamines are formed after concurrent administration of methylamine and nitrite and, if so, whether the nitrosamine formed is carcinogenic.

Three subchronic studies in which animals were exposed to DMA showed that DMA induced relatively minor toxicological changes. In an 8-month study, 3.5 mg/kg DMA was fed to guinea pigs. The only changes noted were an increase in the liver weight and a decrease in phagocytic activity (Dzhanashvili, 1967). Rats, guinea pigs, rabbits, dogs, and monkeys were exposed to 9 mg/m$^3$ for 90 days via inhalation. The author concludes that the animals showed no signs of toxicity; all hematologic values were normal, but some rabbits and monkeys did show dilation of the bronchi (Coon et al., 1970). Isakova et al. (1971) report that rats exposed to 0.5 or 1 mg/m$^3$ DMA for 3 months had significant increases at both concentrations in the number of cells having an abnormal number of chromosomes. There was a normal incidence of structural chromosome breakage, however.

Like other alkylamines, dimethylamine may become nitrosated at an appropriate pH level. Ishiwata et. al. (1975) reported that dimethylnitrosamine (DMNA) was formed in human saliva cultivated with DMA, nitrite, and glucose for 24 hr. Thus *in vivo* formation of DMNA is a real possibility in humans.

Dimethylnitrosamine administered orally at 2 ppm induced tumors in nearly all the rats after 60 weeks. In a 78-day study, rats were exposed orally to nitrite (up to 5 g/l) and DMA (up to 4 cc/l). No tumors were observed, but there were some skin and eye irregularities which the author explained by the depressed vitamin A level in the liver. In a longer experiment, the nitrite levels were increased to 30 g/l. Some rats in the high-nitrite group died of methemoglobinemia, had a similar skin disorder, and had no tumors. The rats in the 5-g/l nitrite group were slaughtered after 410 days and also had low liver vitamin A levels. Two had liver tumors; one had a very large tumor and additional tumors in the spleen and mesentery. The author concluded that all tumors were metastatic sarcomas and not cancers. None of the controls developed tumors (Oka et al., 1974). Epstein (1972) did a similar set of experiments in which he fed various doses of nitrites and DMA concurrently to mice. At 100 mg/kg nitrite and 2,500 mg/kg DMA, centrilobular necrosis, similar to that induced by the administration of DMNA alone, was observed. Exposure to DMA alone had no toxic effects, and liver toxicity was reduced when two compounds were consumed sequentially. The combination of nitrite and DMA also inhibited the synthesis of liver protein in a dose-dependent manner.

In a host-mediated assay using mice and Salmonella, DMA (via oral gavage) and nitrite (per os) increased the mutation rate by a factor of four. This increase is significant, though comparatively modest. For each compound alone, water served as control (Couch and Friedman, 1975). In the only reference concerned with monomethylamine and nitrite, Hussain and Ehrenberg (1974) report that the combination is mutagenic to E. coli. Neither is mutagenic alone.

## Environmental Aspects

Great efforts have been expended to measure environmental levels of methylamines and nitrosamines. Although methylamines occur both naturally and as a result of manufacturing activities, it has proven extremely difficult to determine if there is any health hazard involved in environmental formation of nitrosamines. Recent technological advances have made it possible to measure nitrosamine concentrations at ppb levels; again, the significance of exposure to these low levels is not clear.

### Air

An article from industry points out that since methylamines have such a disagreeable odor, scrubbers are used to remove the methylamines from the stack effluents. Thus emissions are probably minimal (Painst, 1961).

Fine (1976) measured DMNA levels in Belle, W. Va., site of several amine plants, as 5-170 ng/m$^3$ and in Baltimore as 3-320 ng/m$^3$. Near a 1,1-dimethylhydrazine plant in Baltimore he found a high of 36 x 10$^3$ ng/m$^3$; it was later determined that there was a DMNA source on the site. Fine concluded that DMNA may be a low-level impurity of DMA.

Hanst (1977) conducted air chamber studies in which he demonstrated that the rate of nitrosation of DMA in air is too slow to allow for a buildup of DMNA. DMNA decomposes rapidly in UV light; its half-life in sunlight is 30 min, so there is little likelihood that DMNA is a daytime air pollutant. Degradation products from the photolysis of DMNA include formaldehyde, formic acid, DMA, MMA, and methylhydrazine (Grilli et al., 1975). However, DMNA formation may occur at night, especially in polluted ($NO_x$) air. Hanst concluded that any DMNA in air is probably due to direct emissions. An unpublished EPA study (Cohen and Bachman, 1977) concurs with Hanst's conclusion that DMNA is not formed in the air. Samples of industrial wastewater contained DMNA; it is not clear whether DMNA was formed during manufacture or was present in the water supply.

### Soil

Tate and Alexander (1974) demonstrated that commercial concentrations of the pesticide dimethyldithiocarbamate degrade to DMNA. Traces of DMNA have been found after application of the pesticide. Dean-Raymond and Alexander (1976) reported that DMNA can enter the food chain due to its mobility in soil and ability to move through the roots to the leaves of spinach and lettuce. The authors note that there is also a potential for accumulation in ground water.

Several experimenters have demonstrated that nitrites and TMA or DMA form DMNA in soils and manures. However, the concentrations required are high, and no DMNA has been found naturally in soils, sewage, or lake water (Mills and Alexander, 1976; Ayanaba and Alexander, 1974; Tate and Alexander, 1976).

### Other

A brief summary of other areas in which methylamines have been found follows. Methylamines are known to be present in fish. On a fully loaded fish boat, a TMA concentration of 59 ppm was measured; men unloading the fish often felt uncomfortable and some fainted (Daalgard et al., 1972). TMA (at 5 ppm) is responsible for the undesirable fishy taste in milk (Von Gunten, 1976). All the methylamines have been detected in cattle feed yards and in facilities using liquid manure (Mosier and Torbit, 1976).

Perhaps the best known example of nitrosamine formation is in treated meats such as bacon, ham, and frankfurters. Nitrite is used to cure these meats, but, on cooking, measurable amounts (high of 39 ppb) of dimethylnitrosamine are formed in bacon (Wasserman et al., 1978; Collins and MacDonald, 1978). It is not known exactly which amines are the precursors to the nitrosamines.

## REFERENCES

Ayanaba, J., and M. Alexander. Transformations of methylamines and formation of a hazardous product, dimethylnitrosamine, in samples of treated sewage and lake water. Environ. Qual. 3(1):83, 1974.

Cohen and Bachman. Measurement of Environmental Nitrosamines. Unpublished paper. 1977.

Coon, R. A., R. A. Jones, L. J. Jenkins, and J. Siegel. Animal inhalation studies on ammonia, ethylene glycol, formaldehyde, dimethylamine, and ethanol. Toxicol. Appl. Pharmacol. 16:646, 1970.

Couch, D. B., and M. A. Friedman. Interactive mutagenicity of sodium nitrite, dimethylamine, methyl urea, and ethyl urea. Mutat. Res. 31:109, 1975.

Daalgard, J. B., F. Denker et al. Fatal poisoning and other health hazards connected with industrial fishing. Br. J. Ind. Med. 29(3):307, 1972.

Dean-Raymond, D., and M. Alexander. Plant uptake and leaching of dimethylnitrosamine. Nature 262(5567):394, 1976.

Dzhanashvili, G. D. Hygiene substantiation of the maximum permissible content of dimethylamine in water bodies. Gig. Sanit. 37(6):12, 1967.

Epstein, S. S. In vivo studies on interactions between secondary amines and nitrites or nitrates. Anal. Form. Proc. Work Conf. (IARC). 1972. p. 109-115.

Fine, D. H., D. P. Rounbehler et al. N-nitrosodimethylamine in air. Bull. Environ. Contam. Toxicol. 15(6):739, 1976.

Gray, J. I., M. E. Collins, and B. MacDonald. Precursors to dimethylnitrosamine in bacon. J. Food. Prot. 41(1):31, 1978.

Grilli, S., M. R. Tosi, and G. Prodi. Degradation of dimethylnitrosamine catalysed by physical and chemical agents. Gann 66(5):481, 1975.

Hanst, P. L., J. W. Spence, and M. Miller. Atmospheric chemistry of N-nitrosodimethylamine. Environ. Sci. Technol. 11(4):403, 1977.

Harwood, H. J. Amines, lower aliphatic. In Kirk-Othmer Encyclopedia of Chemical Technology, vol. 2. New York, John Wiley & Sons, Inc. 1971. p. 116.

Hussain, S., and L. Ehrenberg. Mutagenicity of primary amines combined with nitrite. Mutat. Res. 26(5):419, 1974.

Isakova, G. K., B. Y. Ekshtat, and Y. Y. Kerkis. On studies of the mutagenic properties of chemical substances in the establishment of hygienic standards. Gig. Sanit. 36(11):9, 1971.

Ishiwata, H., A. Tanimura, and M. Ishidate. Studies on in vivo formation of nitroso compounds. V. Formation of dimethylnitrosamine from nitrate and dimethylamine by bacteria in human saliva. Food Hyg. Soc. Jpn. 16(4):234, 1975.

Mills, A. L., and M. Alexander. Factors affecting dimethylnitrosamine formation in samples of soil and water. J. Environ. Qual. 5(4):437, 1976.

MITRE Corp. Environmental Aspects of Atmospheric Nitrosamines. 1976.a

MITRE Corp. Scoring of Organic Air Pollutants. 1976.b*

Mosier, A. R., and S. Torbit. Synthesis and stability of dimethylnitrosamine in cattle manure. J. Environ. Qual. 5(4):465, 1976.

Oka, K., K. Betto, and I. Nishimori. Development of sarcomata in the livers of albino rats given sodium nitrate and dimethylamine. Acta Med. Nagasaki 18(1-4):13, 1974.

Paist, S. S. Air pollution and methylamines. Ind. Water Wastes 6:158, 1961.

Stanford Research Institute (SRI). Chemical Economics Handbook. Menlo Park, Calif. 1975.

Sutton, W. L. Aliphatic and alicyclic amines. In F. A. Patty (ed.), Industrial Hygiene and Toxicology, 2nd ed. New York, Interscience Publishers. 1963.

Tate, R. L., and M. Alexander. Formation of dimethylamine and diethylamine in soil treated with pesticides. Soil Sci. 118(5):317, 1974.

Tate, R. L., and M. Alexander. Microbial formation and degradation of dimethylamine. Appl. Environ. Microbiol. 31(3):399, 1976.

U.S. EPA (1979), Toxic Substances Control Act Chemical Substance Inventory, Office of Toxic Substances, Washington, D.C.

U.S. International Trade Commission (U.S. ITC). Synthetic Organic Chemicals, United States Production and Sales, 1975.

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*This document was prepared for the U.S. Environmental Protection Agency by the MITRE Corp. It is a secondary source and does not cite its primary references. Thus, verification of some information is not possible. The environmental release data were taken from the NSF/Rann Research Program on Hazard Priority Ranking of Manufactured Chemicals.

# CHEMICAL HAZARD INFORMATION PROFILE

## Morpholine

Date of report: November 16, 1977

This chemical was chosen for study because of the exposure potential associated with its use as a boiler water additive.

The following recommendations are made regarding further OTE evaluation of the possible health or environmental hazards of morpholine.

(1) Require TSCA Section 8(a) submissions--Detailed information on production and uses is not currently available.

(2) Require TSCA Section 8(d) submissions--Available information does not provide very extensive coverage of the health aspects of morpholine.

(3) Revise CHIP report and repeat review.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

## Chemical Identity

Morpholine, $OCH_2\text{-}CH_2\text{-}NHCH_2\text{-}CH_2$ (molecular weight, 87.14), is a colorless, volatile, alkaline, hygroscopic liquid with an amine-like odor. It is miscible with water (some heat is evolved), but does not form a morpholine/water azeotrope. Morpholine is also very soluble in acetone, benzene, ether, methanol, ethanol, and numerous other solvents. Morpholine melts at -4.9°C and boils at 128.9°C. It has a density of 1.002 g/ml at 20°C. The flash point of morpholine is 38°C (100°F) by the open-cup method. Morpholine is flammable and a moderate fire risk.

Synonyms for morpholine include diethylene oximide, diethylene imidoxide, and tetrahydro-1,4-oxazine. Morpholine undergoes reactions typical of a secondary amine. Morpholine's desirable characteristics include reactivity (which is enhanced by the ring structure), mild alkalinity, good solvent properties (due, in part, to the ether oxygen), and a medium boiling point.

## Production and Use

Morpholine annual production capacity is 15 million lb. The producer is Jefferson Chemical Co. (a subsidiary of Texaco Inc.). Dow has had a 5 million lb/year plant on standby since mid-1972. Union Carbide was scheduled to shut down their 15 million lb/year plant at the end of 1974. The demand for morpholine was 24 million lb/year in both 1973 and 1974. In 1974 the price was 65$ per pound delivered in tanks in the East.

Morpholine can be made by reaction of ethylene oxide and ammonia (Hawley, 1977). Other established manufacturing methods are (1) by dehydration of diethanolamine, (2) by reaction of diethylene glycol with ammonia in the presence of hydrogen, an appropriate catalyst, and high temperature and pressure, and (3) by heating bis(2-chloroethyl)ether and anhydrous ammonia in benzene solution in a closed vessel at 50°C for 24 hr (Kirk-Othmer, 1967).

Morpholine is used in rubber chemicals (especially accelerators) 33%; corrosion inhibitors, 25%; optical brighteners for detergents, 10%; alkyl morpholines, 10%; waxes, polishes, and cleaners, 8%; exports, 7%; and miscellaneous, 7%.

Specific applications implied by these categories include use of morpholine as a solvent, use in organic synthesis (especially of pharmaceuticals), use as a boiler water additive, and use in the preservation of book paper (Chemical Marketing Reporter, 1974; Hawley, 1977). Morpholine salts of fatty acids may be used as a component of a protective coating applied to fruits and vegetables (permitted under the Federal Food, Drug, and Cosmetic Act) (Kirk-Othmer, 1967).

## Health Aspects

The recommended TLV for morpholine is 20 ppm time weighted average (70 mg/m$^3$). Caution is often recommended because morpholine can be absorbed through the skin. The single oral LD$_{50}$ for rats is 1,050 mg/kg. The single dermal LD$_{50}$ for 24-hr skin contact is 0.5 mg/kg. Oral administration of 6,330 mg/kg (total dose) over 28 weeks of continuous administration causes neoplastic effects and serves as the TDLo (ITII, 1976).

Investigations were conducted by Shea (as described in ACGIH, 1971) utilizing commercial-grade morpholine (98% pure) in inhalation studies on rats. The notable effects were nasal and bronchial irritation and liver and kidney damage. Rats were exposed to 18,000 ppm for 8 hr daily. One animal died after the 1st day. Its liver and kidney showed congestion and a cloudy swelling. All exposed animals developed violently reddened thoracic walls. A second rat died the 3rd day from lung and kidney congestion. A third rat died on day 4, showing degeneration of the epithelial lining of the kidney tubules. Three rats died after termination of exposure on day 5.

Thickened alveoli, emphysematous areas, incipient necrosis of kidneys and areas of degeneration, fatty changes, and cellular necrosis of the liver were noted. When Shea (reference unknown) was exposed to 12,000 ppm morpholine, he noted nose irritation after 1 min and coughing after 1.5 min. The transfer of morpholine by pipette caused a severe sore throat and reddened mucous membranes. These symptoms cleared upon cessation of this experiment.

## Environmental Aspects

It is estimated that the fraction of dispersion of morpholine is 0.50; an additional 0.03 is lost in production. Thus an estimated 53% of morpholine produced is dispersed (12.4 million lb/year if production is estimated at 23.3 million lb/year) (Dorigan et al., 1976).

## REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). Documentation of TLV's. 1971.

Chemical Marketing Reporter. June 3, 1974.

Dorigan, J. et al. Scoring of Organic Air Pollutants. MITRE Corp. 1976.*

Hawley, G. G. (ed.). Condensed Chemical Dictionary, 9th ed. New York, Van Nostrand Reinhold Co. 1977.

ITII (International Technical Information Institute). Toxic and Hazardous Industrial Chemicals Safety Manual. Tokyo. 1976.

Kirk-Othmer Encyclopedia of Chemical Technology. New York, John Wiley & Sons, Inc. 1967.

The Merck Index, 8th ed. Rahway, N.J., Merck and Co., Inc. 1963.

Sax, N. Irving (ed.). Dangerous Properties of Industrial Materials, 3rd ed. New York, Van Nostrand Reinhold Co. 1977.

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# CHEMICAL HAZARD INFORMATION PROFILE

## 2-Nitropropane

Date of report: September 27, 1977

This chemical was chosen for study because of carcinogenic activity reported in a NIOSH Current Intelligence Bulletin.

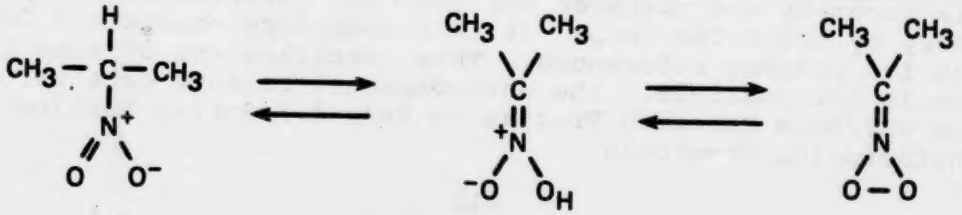
It is recommended that 2-nitropropane proceed to a PRL I assessment. Evidence of carcinogenicity in test animals and toxic effects observed in workers exposed to 2-nitropropane imply that it may present serious health problems. Requiring TSCA Section 8(a) and 8(d) submissions is recommended in order to provide a better base of information for PRL I assessment.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

### Chemical Identity

2-Nitropropane is a clear, colorless liquid with a pleasant odor. Its molecular formula is $CH_3CH(NO_2)CH_3$. It has a molecular weight of 89.09. Synonyms for 2-nitropropane include dimethylnitromethane, isonitropropane, nitroisopropane, and 2NP; it is marketed under names such as NiPar S-20. The melting point of 2-nitropropane is -93°C; the boiling point is 120.3°C. It is slightly soluble in water (1.7 ml/100 ml of water at 25°C). Water is soluble in 2-nitropropane (0.6 ml water/100 ml of 2NP). Nitropropane dissolves in many solvents, including chloroform. The specific gravity of 2-nitropropane is 0.992. Its vapor pressure is 20 mm Hg at 25°C (13 mm Hg at 20°C). Its ignition temperature is 802°F (Browning, 1965). Its vapors make for an explosive mixture with air. The lower flammability limit is 2.6% by volume in air (upper limit unknown). 2-Nitropropane exists in equilibrium with 2-propane nitronic acid:



At equilibrium one finds a much higher concentration of the true nitro compound. 2-Nitropropane also exists as aci-2-nitropropane (a derivative of the sodium salt).

## Production and Use

The vapor-phase reaction between propane and nitric acid vapor gives crude 2-nitropropane. The reaction is carried out at 370 to 450°C and 8 to 12 atmospheres pressure in stainless-steel apparatus. The reaction products are cooled. The various nitropropanes and the associated by-products of aldehydes and ketones condense while the nitric oxide and unreacted propane remain as vapor. The propane is separated from the nitric oxide and recycled. Nitric oxide is removed for conversion to air, water, and nitric acid (which reenters the system). The crude 2-nitropropane is washed and sent to fractionation towers for separation by distillation (Kirk-Othmer, 1967).

2-Nitropropane has been commercially available since 1940 from Commercial Solvents Corp. (recently acquired by IMC Corp.). It is produced at their plant in Sterlington, La. Twelve million of the estimated 30 million lb of 2-nitropropane produced annually is sold domestically; the remainder is either used internally at IMC or exported (HEW/NIOSH, 1977). Major distributors of 2-nitropropane (other than Commercial Solvents Corp.) include Amsco Division of Union Oil Co. of California, Ashland Chemical Co. (Industrial Chemicals and Solvents Division), and Thompson Hayward Chemical Co. (Finklea, 1977).

2-Nitropropane is used in manufacturing as a solvent for organic compounds, cellulose, esters, resins, gums, vinyl resins, waxes, epoxy, fats, dyes, and chlorinated rubber. Desirable qualities which 2-nitropropane contributes to solvent systems include improved drying time, more complete solvent release, better flow and film integrity, greater wetting ability, improved electrostatic spraying, and increased pigment dispersion. It is used as a solvent for printing on polyvinyl films. 2-Nitropropane is utilized in the coating industry, where its use showed a rapid increase at least up to the early 1960's. Its combustion properties have made it useful as a rocket propellant and as a gasoline and diesel fuel additive. 2-Nitropropane also has limited use as a paint and varnish remover. It serves as an intermediate in organic synthesis of some pharmaceuticals, dyes, insecticides, and textile chemicals.

Nitroparaffins have been used for fuels in model engines and short-distance racing cars since at least the mid-1950's and up to at least the mid-1960's. Such racing car fuels might contain 20% 2-nitropropane. 2-Nitropropane and 2,2-dinitropropane have been tested as rocket propellants. 2-Nitropropane gives both desirable physical properties and relative ease of handling and availability. The addition of as little as 0.1 to 0.2% by weight of 2,2-dinitropropane increases the octane rating of diesel fuel from 5 to 10 units. Nitropropane is especially useful as a fuel additive when extra power may be needed for short periods of time. It increases power output and reduces the smoke coming from the exhaust. This has important potential for air pollution abatement (Kirk-Othmer, 1967).

The major uses of 2-nitropropane as stated by sources at IMC are as a solvent in industrial coatings and in printing inks. 2-Nitropropane is used internally by IMC for conversion to nitro compounds including aminohydroxy compounds. IMC also sells 2-nitropropane abroad. (NIOSH estimates that 100,000 workers are potentially exposed to 2-nitropropane [Finklea, 1977]. Sources at IMC claim that a maximum of 15,000 persons are exposed.)

## Health Aspects

### General

The trend in the evaluation of the toxicity of 2-nitropropane has been toward considering it as an increasingly dangerous substance. In 1962 the American Council of Governmental Industrial Hygienists (ACGIH) recommended 50 ppm as the maximum acceptable occupational exposure for 2-nitropropane. By 1971, this was changed to 25 ppm, which is the current OSHA standard for occupational exposure. Based on their most recent studies, NIOSH currently recommends handling 2-nitropropane as if it were a carcinogen (Finklea, 1977).

The TLM aquatic toxicity rating for 2-nitropropane (96-hr exposure) is 10-100 ppm; this is considered a "slightly toxic" rating (NIOSH, 1976).

### Humans (General)

Generally observed symptoms in humans exposed to 2-nitropropane vapors include anorexia, nausea, vomiting, diarrhea, severe occipital headaches, cyanosis, and vapor irritation of the lungs. Large doses have the potential of producing methemoglobinemia and damaging the liver and kidneys. Other toxic effects on the central nervous system may arise. 2-Nitropropane cannot be detected in humans by odor at 83 ppm (Sutton, 1963).

## Human Exposure

There are report sources that five or six workers dipping forms into a solvent mixture of vinyl copolymer dissolved in xylene and ~20% 2-nitropropane (at 110 to 120°F and occasionally 150°F) developed anorexia, nausea, vomiting, and occasional diarrhea. Symptoms were not present before exposure, but would arise as the workday progressed. Workers had no symptoms on holidays. The exposure level in the work area was approximately 20 to 45 ppm of 2-nitropropane (no xylene concentration given). Substitution of methyl ethyl ketone relieved the symptoms (Browning, 1965).

Workers exposed to concentrations of 10 to 30 ppm of 2-nitropropane for not more than 4 hr per day, 3 days per week, in a spraying operation (utilizing lacquer with 20% 2-nitropropane) experienced no ill effects (Sutton, 1963).

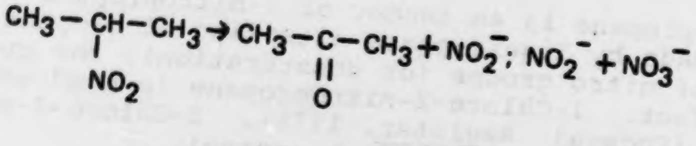
A report source on two workers attributes the death of one, and liver damage in both, to high-level exposure to 2-nitropropane while painting the inside of a tank (Finklea, 1977, refers to Gaultier et al., Arch. Mal. Prof. 25:425, 1964).

In another report source, workers exposed to from 165 to 445 ppm mixed 1- and 2-nitropropane experienced nausea, dizziness, headaches, and diarrhea (Finklea, 1977, refers to Documentation of Threshold Limit Values, American Conference of Governmental Industrial Hygienists, 1971).

Williams et al. (1974) reported an excess of toxic hepatitis among construction workers applying epoxy resins to the walls of a nuclear power plant. Although the hepatitis in this case was attributed to exposure to a known hepatotoxin, p,p'-methylene-dianiline, these men had also used 2-nitropropane to remove hardened resin from their skin (Finklea, 1977).

## Animals

The primary route of absorption of nitroparaffins (including 2-nitropropane) is through the lungs and the gastrointestinal tract; no symptom-producing absorption is known to occur through the skin. Mononitroparaffins disappear from the blood rapidly after absorption. A portion is excreted unchanged in expired air, and a portion is metabolized with resulting formation of $NO_2^-$ and $NO_3^-$ (found in blood and urine). The overall reaction *in vivo* appears to be:



$$CH_3-\underset{NO_2}{\underset{|}{CH}}-CH_3 \rightarrow CH_3-\underset{O}{\underset{||}{C}}-CH_3 + NO_2^-;\ NO_2^- + NO_3^-$$

Lethal dosage depends on concentration and length of exposure. Studies have been done on measured exposure to 2-nitropropane using monkeys, cats, rabbits, rats, and guinea pigs. Experimentally, cats were most sensitive to 2-nitropropane; guinea pigs were least sensitive. Exposure to high concentrations of 2-nitropropane caused dyspnea, cyanosis, prostration, some convulsions, lethargy, and weakness, proceeding to coma and death. In cats and rats, coma and death followed in a short time, while rabbits and guinea pigs died 1 to 4 days after apparent partial recovery. Severe exposure caused 60 to 80% methemoglobin in cats. Heinz body formation was also more frequent in cats. Exposure of cats to 328 ppm caused prothrombin reduction and increased clotting time. Livers of cats that died after exposure to several periods of 328 ppm showed severe degeneration and focal necrosis. Cats exposed to 328 ppm 2-nitropropane showed degeneration in heart and kidneys and cerebral neuron disintegration. The lungs showed pulmonary edema, intraalveolar hemorrhage, and interpneumonitis. Other species exposed to this concentration did not exhibit these symptoms. Cats developed 25 to 35% methemoglobin when exposed to 750 ppm for 4.5 hr; they showed 15 to 25% methemoglobin when repeatedly exposed to 280 ppm for 7 hr per day. Heinz bodies appeared in the erythrocytes of cats and rabbits at even lower concentrations (Browning, 1965).

The most recent studies on the effects of 2-nitropropane inhalation were conducted by the Huntingdon Research Center for NIOSH (HEW/NIOSH, 1977). It involved exposing rats and rabbits to commercial-grade 2-nitropropane for 7 hr per day, 5 days per week. One group was exposed to 207 ppm 2-nitropropane; a second group was exposed to 27 ppm; a third group was as a control. The rats exposed to 207 ppm 2-nitropropane were weanling rats (younger and smaller than the other exposed rats and the control group). They were introduced to replace rats experiencing excess mortality during the first few days of exposure to 400 ppm 2-nitropropane. Also, food and water were present during exposure in all cases, adding the potential for oral intake of 2-nitropropane (Finklea, 1977). Animals were killed at intervals in order to evaluate the effects of 2-nitropropane exposure. Liver neoplasms, described as hepatocellular carcinoma or hepatic adenoma, were observed in all rats killed after 6 months of exposure to 207 ppm 2-nitropropane. No tumors were observed in any other animals in this study, including controls. Further investigation of the toxicity of 2-nitropropane was begun in April 1977 under the sponsorship of the IMC Chemical Group, Inc. (Finklea, 1977).

## Specific Related Compounds

1-Nitropropane is an isomer of 2-nitropropane. 2,2-Dinitropropane is made by liquid-phase nitration of propane. The greater the number of nitro groups (or unsaturation), the greater the irritant effect. 1-Chloro-2-nitropropane is used as a soil fungicide. (*Federal Register*, 1971). 2-Chloro-1-nitropropane has been found useful in starfish control.

Environmental Aspects

No information was found in the sources consulted on the environmental fate or effects of 2-nitropropane.

## REFERENCES

Browning, Ethel. Toxicity and Metabolism of Industrial Solvents. New York, Elsevier Publishing Co. 1965. p. 283-284.

Federal Register, Rules and Regulations, Part 420, Tolerances and Exemptions from Tolerances for Pesticide Chemicals in or on Raw Agricultural Commodities, 1-Chloro-2-Nitropropane. Series 36, issue 175, Sept. 9, 1971, p. 18079-18080.

Finklea, John F. Current Intelligence Bulletin: 2-Nitropropane. National Institute for Occupational Safety and Health. April 25, 1977.

Hawley, G. G. (ed.). The Condensed Chemical Dictionary, 9th ed. New York, Van Nostrand Reinhold Co. 1977.

HEW/NIOSH (1977), Chronic Inhalation Exposure of Rats and Rabbits to Nitromethane and 2-Nitropropane, Project No. 210-75-0039.

International Technical Information Institute. Toxic and Hazardous Industrial Chemicals Safety Manual. Tokyo. 1976. p. 377-378.

Kirk-Othmer Encyclopedia of Chemical Technology, 2nd ed., vol. 13. New York, John Wiley & Sons, Inc. 1976. p. 864-883.

The Merck Index, 8th ed. Rahway, N.J., Merck and Co., Inc. 1968.

NIOSH. Registry of Toxic Effects of Chemical Substances, 1976 ed.

Sax, Irving N. Dangerous Properties of Industrial Materials, 3rd ed. New York, Van Nostrand Reinhold Co. 1968.

Steere, Norman V. Hazardous chemicals data. J. Chem. Educ. 45(4):A317-A318, 1968.

Sutton, William L. Aliphatic nitro compounds, nitrates, and nitrites. In Frank A. Patty (ed.), Industrial Hygiene and Toxicology, 2nd ed., vol. 2. New York, Interscience Publishers, Inc. 1963. p. 2000-2079.

Weast, Robert C. (ed.). CRC Handbook of Chemistry and Physics, 52nd ed. Cleveland, The Chemical Rubber Co. 1971.

Williams, S. V. et al. Toxic hepatitis and methylenedianiline. N. Engl. J. Med. 291:265, 1974.

# CHEMICAL HAZARD INFORMATION PROFILE

## 2-Pentanone

Date of report: December 6, 1977

This chemical was chosen for study because of an inquiry about its possible occurrence in a drinking water supply.

No judgment on this chemical is appropriate at this time because of a lack of information.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

### Chemical Identity

2-Pentanone ($C_5H_{10}O$) is a clear liquid with a strong odor resembling acetone and ether. It melts at -83.5°C and boils at 102°C. The vapor pressure of 2-pentanone is 16 mm Hg at 20°C; its specific gravity is 0.8064 (at 20°C). It is soluble in acetone and in ether and is slightly soluble in water (5.5 g/100 g). 2-Pentanone is flammable from 1.55% to 8.15% by volume in air. Synonyms for 2-pentanone include methyl n-propyl ketone, ethyl acetone, and methyl propyl ketone. (Browning 1965; Patty 1963).

### Production and Use

The major method of production of 2-pentanone is by oxidation of 2-pentanol. 2-Pentanone is used as a solvent, especially as a substitute for diethyl ketone. It is used as a solvent in much the same places that acetone is used. 2-Pentanone has also been used as a flavoring (Hawley, 1977). (It has been approved for use as a synthetic flavoring by the FDA [Title 21, 172.515, Code of Federal Regulations].) It is produced by Union Carbide Corp. in West Virginia (SRI, 1975). Due to the fact that there is only one commercial producer of 2-pentanone, no information on production volume or capacity is available.

## Health Aspects

The TLV of 2-pentanone is 200 ppm (ACGIH, 1971). The $LD_{50}$ for oral administration to rats is 3,730 mg/kg. The 4-hr inhalation $LC_{50}$ is 2,000 ppm for rats (NIOSH, 1976). 2-Pentanone vapors irritate the eyes and respiratory tract. At high concentrations it acts as a narcotic (ITII, 1976). No toxic effects have been reported from industrial use.

Absorption through the skin has been observed with 2-pentanone. Elimination takes place mainly unchanged in expired air (estimated 38 to 54% expelled in air in 25 to 35 hr). The rate of elimination of 2-pentanone from the blood is only half as fast as that of 2-pentanol. 2-Pentanone may be excreted in combination with glucuronic acid. 2-Pentanone is the major metabolite of 2-pentanol (Browning, 1965). No references were found pertaining to the mutagenicity or carcinogenicity of 2-pentanone.

## Environmental Aspects

No information was found on environmental aspects of 2-pentanone.

## REFERENCES

American Conference of Governmental Industrial Hygienists (ACGIH). Documentation of TLV's. 1971.

Browning, Ethel. Toxicity and Metabolism of Industrial Solvents. Amsterdam, Elsevier Publishing Co. 1965.

Hawley, G. G. (ed.). Condensed Chemical Dictionary, 9th ed. New York, Van Nostrand Reinhold Co. 1977.

ITII (International Technical Information Institute). Toxic and Hazardous Industrial Chemicals Safety Manual. Tokyo. 1976.

NIOSH. Registry of Toxic Effects of Chemical Substances, 1976 ed.

Patty, Frank A. (ed.). Industrial Hygiene and Toxicology. New York, Interscience Publishers, Inc. 1963.

SRI (Stanford Research Institute). Directory of Chemical Producers. Menlo Park, Calif. 1975.

# CHEMICAL HAZARD INFORMATION PROFILE

## Phenylenediamines

Date of report: June 1, 1978

This group of chemicals was chosen for study because of the exposure potential associated with its use pattern and the structural relationship of these chemicals to known carcinogens.

It is recommended that judgment be deferred on phenylenediamines due to insufficient information. Additional information which should be obtained before making a judgment includes:

(1) Results of NCI carcinogenicity study.

(2) Production volume from TSCA inventory.

(3) Use information through Section 8(a).

(4) Relevant information obtained by the Interagency Testing Committee in its review of these compounds.

(5) Update this CHIP based upon the additional information obtained.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

### Chemical Identity

There are three isomers of phenylenediamine, the ortho, meta, and para forms. All the isomers are crystalline solids at room temperature and are soluble in water, alcohol, ether, and benzene.

| CAS no. | Chemical name | Melting pt. (°C) | Vapor pressure | Log P |
|---|---|---|---|---|
| 95-54-5 | Ortho-phenylene-diamine (o-PDA) | 102 | Neg. | .37 |
| 108-45-2 | Meta-phenylene-diamine (m-PDA) | 65 | - | - |
| 100-50-3 | Para-phenylene-diamine (p-PDA) | 140 | 1 mm Hg/ 98.8°C | .26 |

Source: Adapted from Weast, 1971, and MITRE Corp., 1976.

## Production and Use

This section is based largely on information compiled by Auerbach Associates.

Current production data are not available for phenylenediamines. In 1962, 540,000 lb of o-PDA and 1.4 million lb of m-PDA were produced (Kirk-Othmer, 1968). SRI (1977) lists the annual production of each phenylenediamine as over 1,000 lb. Although production volume appears to be limited, there are 10 manufacturers and processors, and the uses indicate a potential for human exposure. General uses for phenylenediamines include applications as dye intermediates, as oxidation inhibitors in petroleum and rubber products, and as photographic developers. The three compounds are found in a variety of oxidative hair dyes and are also used in dyeing furs. Miscellaneous uses for each compound are listed below:

| | |
|---|---|
| o-PDA | Lab reagent |
| m-PDA | Textile developing agent, corrosion inhibitor, monomer for Nomex Nylon, used in fire-resistant clothing, prepolymer for spandex |
| p-PDA | Ursol, a fur dye, monomer in Fiber B to make tire cord |

Source: SRI, 1975; Kirk-Othmer, 1968.

## Health Aspects

The major issues involved are centered around the use of phenylenediamines in consumer hair dyes. Many hair dyes are mutagens in the Ames system. Long-term industry studies have failed to demonstrate that there is a risk of either cancer or chromosome damage associated with hair dyes. However, most of these studies attempt to replicate patterns of human exposure to hair dyes in rats. Another area of concern is skin sensitization.

### Acute Effects

Although phenylenediamines are fairly toxic when administered subcutaneously, neither m-PDA or p-PDA is very fat soluble and would not normally be expected to enter the body. There are no known cases of industrial poisoning (Hamblin, 1963).

| | | |
|---|---|---|
| LDLo - Subcutaneous - rat | o-PDA | 600 mg/kg |
| | m-PDA | 80 mg/kg |
| | p-PDA | 100 mg/kg |

Source: NIOSH, 1975.

### Skin Sensitization

p-PDA is easily oxidized in air and moisture, and these oxidation products are strong skin sensitizers. Industrial exposure has caused allergic bronchial asthma, Because of skin sensitization, the TLV for p-PDA is 0.01 mg/m$^3$ (ACGIH, 1971).

Two epidemiological surveys indicate that p-PDA is one of the most common skin sensitizers. Using skin allergy patients as subjects, 8% of 1,200 patients reacted to a 1% p-PDA solution in a standard skin patch test. In the other study, a 2% solution of p-PDA induced allergic reactions in 13.5% of the subjects. In addition, there was a strong cross-sensitization to substituted phenylenediamines such as isopropyl-PDA, which is used in rubber and tires (Baer et al., 1973; Rudner et al., 1973). Fisher (1975) studied 20 patients who were strongly sensitized to p-PDA to determine whether they were allergic to hair dyed with p-PDA. None of the patients reacted to the dyed hair.

### Mutagenicity and Chronic Studies

Ames (1975) tested 169 hair dyes and found that 150 were mutagenic in his assay. Some required microsomal activation and others required oxidation with hydrogen peroxide. Both o-PDA and m-PDA were mutagenic in a dose-dependent manner in *Salmonella* strain TA 1538, which detects frameshift mutagens. The para isomer alone was not mutagenic in a variety of *Salmonella* strains. However, when oxidized with peroxide, a highly mutagenic trimer was formed. Under normal hair-dyeing conditions, this reaction product is thought to be a minor constituent, but it can be absorbed through dog's skin. Garner and Nutman (1977) report that all three phenylenediamines are dose-related mutagens in the Ames system with liver activation. The m-PDA caused a 50-fold increase in the spontaneous mutation rate of mouse lymphoma cells (Palmer et al., 1977). Blijleven (1977) found that p-PDA alone is a weak mutagen in *Drosophila melanogaster*. The three compounds were administered orally to males and induced mutations in metabolically active germ cells. Burnett et al. (1977) conducted a dominant lethal assay on rats. Male rats were given 20 mg/kg of o-, m-, or p-PDA intraperitoneally three times a week for 8 weeks. After a brief waiting period they were allowed to mate. The investigators found no statistically significant changes in the numbers of resorptions or live fetuses.

Burnett et al. (1976) found that hair dye which contained 2% p-PDA was not teratogenic to rabbits. Other active ingredients were resorcinol, 2,4-diaminoanisole sulfate, and 2-nitrophenylenediamine. Hair dyes were mixed with peroxide according to directions and were applied to the skin twice a week for 13 weeks. There was no evidence of teratogenicity, systemic toxicity, or lesions; organ weights and blood values were normal. Nine out of 169 fetuses did have abnormalities such as notched or short ribs. In another study (Burnett et al., 1975), hair dye containing p-PDA and m-PDA was applied to mouse skin weekly or biweekly for 18 months. Again, no evidence of carcinogenicity or blood or organ abnormalities was found.

Giles and Chung (1976) conducted a 2-year mouse skin-painting study using 2,4-toluenediamine alone and in combination with p-PDA, resorcinol, and 2,5-TDA. There was a high spontaneous rate of skin and lung neoplasms (15%), and the authors concluded that the treated groups did not have significantly more neoplasms than the controls.

Russian experimenters (Kachalai et al., 1973) found that m-PDA administered orally to rats for 3 to 4 months affected the central nervous system and the detoxification activity of the liver. When applied to the rats' skin, it induced dermatitis. Human subjects exposed to 1 to 2 µg/l (route and duration not stated) developed pathological liver and kidney changes.

NCI has completed a bioassay on the hydrochloride salt of p-phenylenediamine and is drafting a report.

## Environmental Aspects

No information was found concerning the environmental aspects of phenylenediamines. Since they are easily oxidized, they would not be expected to persist in the air or water. Their low partition coefficients indicate little potential for bioaccumulation.

## SUPPLEMENT

Very little information was available concerning phenylenetriamines; instead of writing a separate profile, this supplements the profile of phenylenediamines.

## Chemical Identity

The melting point of 1,2,3-phenylenetriamine is 103°C and it is soluble in water, alcohol, and ether (Weast, 1971).

## Production and Use

It appears that 1,3,5-triaminobenzene may be the only isomer of commercial importance; however, production figures were not available. It is primarily used as an intermediate in the production of phloroglucinol (1,3,5-trihydroxybenzene), which is used in the dye and reproduction process industries. Other applications include use as an ion exchange resin intermediate, as a photographic developer (CCD, 1971; Kirk-Othmer, 1968), and as a wetting and frothing agent.

## Health Aspects

Garner and Nutman (1977) reported that after liver activation 1,2,4-triaminobenzene is a strong mutagen in *S. typhimurium* TA 1538, which detects frameshift mutations. This compound is a possible degradation product of chrysoidine, an azo dye known as Basic Orange 2, which is a mouse carcinogen.

## REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). Documentation of Threshold Limit Values. Cincinnati. 1971.

Ames, B. A., H. D. Kammen, and E. Yamasaki. Hair dyes are mutagenic: Identification of a variety of mutagenic ingredients. Proc. Natl. Acad. Sci. U.S.A. 72(b):2423, 1975.

Baer, R. L., D. L. Ramsey, and E. Biondi. The most common contact allergens. Arch. Dermatol. 108:74, 1973.

Blijleven, W. G. H. Mutagenicity of four hair dyes in Drosophila melanogaster. Mutat. Res. 48:181, 1977.

Burnett, C., E. I. Goldenthal et al. Teratology and percutaneous toxicity studies on hair dyes. J. Toxicol. Environ. Health 1:1027, 1976.

Burnett, C., B. Lanman et al. Long-term toxicity studies on oxidation hair dyes. Food Cosmet. Toxicol. 13:353, 1975.

Burnett, C., R. Loehr, and J. Corbett. Dominant lethal mutagenicity study on hair dyes. J. Toxicol. Environ. Health 2:657, 1977.

Chemical Week (October 1977), 1978 Buyer's Guide Issue, Part 2, p. 550.

Condensed Chemical Dictionary (CCD), 8th ed. New York, Van Nostrand Reinhold Co. 1971. p. 680.

Fisher, Alexander. Is hair dyed with para-phenylene-diamine allergenic? Contact Dermatitis 1(4):226, 1975.

Garner, R. C., and C. A. Nutman. Testing of some azo dyes and their reduction products for mutagenicity using Salmonella typhimurium TA 1538. Mutat. Res. 44:9, 1977.

Giles, A. L., and C. W. Chung. Dermal carcinogenicity study by mouse-skin painting with 2,4-toluenediamine alone or in representative hair dye formulations. J. Toxicol. Environ. Health 1:433, 1976.

Hamblin, D. O. Aromatic nitro and amino compounds. In Frank A. Patty (ed.), Industrial Hygiene and Toxicology, vol. II. New York, Interscience. 1963. p. 2105-2169.

Kachalai, D. P. et al. Effect of m-phenylenediamine on internal organs and the nervous system. Farmakol. Toksikol. 73:180-183, 1973. (Abstract)

Kirk-Othmer Encyclopedia of Chemical Technology, 2nd ed., vol. 15. New York, John Wiley & Sons. 1968.

MITRE Corp. Scoring of Organic Air Pollutants. 1976.*

NIOSH. Registry of Toxic Effects of Chemical Substances. 1975.

Palmer, K. A., A. Denuzo, and S. Green. The mutagenic assay of some hair dye components using the thymidine kinase locus of L5 1178Y mouse lymphoma cell. J. Environ. Pathol. Toxicol. 1(1):87, 1977. (Abstract)

Rudner, E. J., W. E. Clendenning et al. Epidemiology of contact dermatitis in North America: 1972. Arch. Dermatol. 108: 537, 1973.

SRI (Stanford Research Institute). Chemical Economics Handbook. Menlo Park, Calif. 1975.

SRI. A Study of Industrial Data on Candidate Chemicals for Testing. August 1977.

Weast, Robert C. (ed.). Handbook of Chemistry and Physics, 52nd ed. Cleveland, Ohio, Chemical Rubber Co. 1971.

Windholz, Martha. The Merck Index, 9th ed. Rahway, N.J., Merck and Co. 1976. p. 947-948.

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*This document was prepared for the U.S. Environmental Protection Agency by the MITRE Corp. It is a secondary source and does not cite its primary references. Thus, verification of some information is not possible. The environmental release data were taken from NSF/Rann Research Program on Hazard Priority Ranking of Manufacturing Chemicals.

# CHEMICAL HAZARD INFORMATION PROFILE

## Phosgene

Date of report: June 13, 1977

This chemical was chosen for study because it was mentioned as a possible cause for "Legionnaire's disease." Chlorofluorocarbons were reportedly combusted at burning cigarette tips with phosgene generation leading to the observed respiratory problems.

It is recommended that phosgene be considered for testing. Very little information is available concerning the effects of chronic exposure to phosgene. Knowledge of chronic effects is important because of phosgene's presence as a common air pollutant. It is also recommended that a Chemical Hazard Information Profile be prepared on chloroacyl chlorides since they can be formed from the same precursors (chlorinated hydrocarbons) as phosgene.

Note: It was found that phosgene was not the cause of "Legionnaire's disease."

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

### Chemical Identity

Phosgene, $COCl_2$, is a colorless gas at normal temperature and pressure with a characteristic sweet odor at low concentrations. Phosgene is slightly soluble in water, where it hydrolyzes to form HCl and $CO_2$. It is soluble in carbon tetrachloride, chloroform, benzene, and other organic solvents (NIOSH, 1976). Phosgene is a heavy gas (3.4 times as heavy as air) and settles readily in low places (Hardy, 1964).

### Production and Use

Most commercially produced phosgene is used captively because of its great toxicity. Phosgene is manufactured in the following manner: purified carbon monoxide is mixed with purified chlorine gas (equimolar or slight excess of CO) and allowed to react over activated charcoal; the phosgene reaction product is subsequently purified and condensed (Hardy, 1964). See Table 1 for annual production figures.

Table 1. Annual Production of Phosgene[a] (millions of lb)

| | |
|---|---|
| 1960 | 37 |
| 1965 | 285 |
| 1970 | 618 |
| 1973 | 728 |

[a] Less than 2% of all phosgene produced is used for the merchant market (CEH, 1975).

Phosgene is used most extensively in the production of toluene diisocyanate (TDI). TDI is a precursor of polyurethane resins which are used to make foams, elastomers, and coatings. A rapidly growing use of phosgene is in the manufacture of polymethylene polyphenylisocyanate (PMPPI), which is used in the production of rigid polyurethane foams. Polycarbonate resins are also based on phosgene and find use as appliance and electrical tool housings, electronic parts, and break-resistant glazing. Refer to Table 2 for other uses and an outline of the consumption pattern (CEH, 1975).

Table 2. Consumption of Phosgene (%)

| | 1965 | 1969 | 1970 | 1973 |
|---|---|---|---|---|
| TDI[a] | 66 | 62 | 64.5 | 61.7 |
| PMPPI | 5.5 | 17 | 16 | 23.6 |
| Polycarbonate resins | 2 | 2.5 | 2.6 | 3.9 |
| Other[b] | 26.5 | 18.5 | 16.7 | 10.7 |

[a] This category includes only the 80/20% (by weight) toluene-2,4-diisocyanate/toluene-2,6-diisocyanate mixture.

[b] Additional uses for phosgene include the production of acyl chlorides, chloroformate esters, diethyl carbonate, dimethyl carbamyl chloride, and isocyanates other than TDI and PMPPI; phosgene is also used in the manufacture of dyes, biocides, and pharmaceuticals and as a chlorinating agent (CEH, 1975).

## Health Aspects

### Human Toxicity

Human exposure to phosgene reported in the literature is generally limited to episodes of acute overexposure. There are no pertinent data available concerning the effects of chronic low-level exposure to phosgene.

Phosgene concentrations of 3 to 5 ppm cause eye and throat irritation; 25 ppm is dangerous when exposure lasts from 30 to 60 min, and 50 ppm is rapidly fatal after short exposure. Phosgene poisoning is characterized by a symptom-free latent period of 2 to 24 hr followed by chest pain, shortness of breath, and increasing difficulty in breathing. Severe exposures may lead to rapid pulmonary edema, which destroys the lung lining and the capacity for oxygen exchange. Death may occur within 36 hr or less following exposure. In nonfatal cases, no permanent residual damage is thought to occur (Sax, 1968; Patty, 1963).

### Laboratory Animal Toxicity

Acute overexposure to phosgene for short periods of time generally produces the same symptoms in all animal species tested. Animals that succumb following exposure display severe pulmonary edema. Survivors of an acute episode show varying amounts of bronchopneumonia, benign pneumonia, bronchial plugging, lung collapse, pulmonary consolidation, pneumonia, and emphysema (NIOSH, 1976).

Cameron et al. (1942) exposed six mammalian species to 0.2 ppm (0.9 $mg/m^3$) of phosgene for 5 hr daily over 5 consecutive days. No deaths occurred from the acute exposure, and few animals displayed any evidence of distress. Necropsy revealed pulmonary lesions in 67% of the animals, with an estimated 5 to 10% exhibiting moderately severe lesions. Pulmonary edema was noted in 41%, but was slight in most cases. Repeated exposure at low concentration was concluded to induce lung damage, though rarely to a severe degree.

### Hygienic Standards

International hygienic standards are as follows: United States, East Germany, and Czechoslovakia, 0.4 $mg/m^3$ (8-hr TWA for a 40-hr week); West Germany, 0.5 (8-hr TWA for a 40-hr week); Sweden, 0.2 (ceiling concentration); U.S.S.R., 0.5 (ceiling concentration) (Winell, 1975).

## Environmental Aspects

### Atmospheric Formation

The three most readily identifiable sources of phosgene in air are direct emissions of phosgene during industrial production or use, thermal decomposition of chlorinated hydrocarbons, and atmospheric photooxidation of chlorinated hydrocarbons. The first two sources are likely to represent a significant indoor hazard, but their contribution to the atmospheric budget is minimal (Singh, 1976). Photooxidation of chlorinated hydrocarbons appears to represent the most probable source of ambient levels of phosgene.

Singh et al. (1975) reported that simulated tropospheric irradiation of perchloroethylene in air over a period of 7 days produced carbon tetrachloride (8% by weight) and phosgene (70 to 80% by weight). Rough calculations based on these figures and the estimated worldwide emissions of perchloroethylene (450 x $10^6$ kg/year) suggested an annual atmospheric phosgene loading of between 315 and 382 x $10^6$ kg/year. Gay (1976) reported that 1,1-dichloroethylene and trichloroethylene as well as perchloroethylene can be photooxidized (in the lab) to form phosgene and other reaction products (including the corresponding mono-, di-, and trichloroacetyl chlorides). Reactivity was in the order of 1,1-dichloroethylene>trichloroethylene>perchloroethylene. Spence et al. (1976) experimentally demonstrated the formation of phosgene following the irradiation of both methylene chloride and chloroform.

Singh (1976) proposes that the photooxidation of chloroethylenes, particularly trichloroethylene and perchloroethylene, is the primary source of atmospheric phosgene. The cited article includes the first reported measurements of phosgene in the ambient air. The phosgene values and those of the chloroethylene precursors may be found in Table 3. The highest phosgene and precursor concentrations are found, as expected, at the urban monitoring locations. Because of the high chloroethylene emissions encountered in urban areas and the relatively reactive nature of the precursors in the atmosphere, the author feels that high phosgene concentrations in urban centers could occur during adverse weather conditions and thereby result in a health hazard. Laboratory studies also suggest that toxic di- and trichloroacetyl chlorides would together be present at about four times the level of phosgene. The author concludes that the continuous release of chloroethylenes to the atmosphere in large quantities may represent a health hazard because of the toxicity of phosgene and chloroacetyl chlorides, in addition to the toxicity inherent in chloroethylenes.

Table 3. Measured Phosgene and Precursor Levels in California[a]

| Nature of site | $COCl_2$ | $C_2Cl_4$ | $C_2HCl_3$ |
|---|---|---|---|
| Urban (Los Angeles) | 31.7[b] | 673.3 | 310.8 |
| | (8.3)[c] | (496.8) | (301.6) |
| | (max. 61.1) | | |
| Downwind of urban Los Angeles | 29.3 | 278.1 | 39.7 |
| | (6.2) | (232.7) | (83.6) |
| | (max. 44.4) | | |
| Remote, high altitude (Badger Pass) | 21.6 | 30.7 | 15.6 |
| | (5.1) | (10.5) | (2.5) |
| | (max. 28.8) | | |
| Urban-suburban (Menlo Park) | 30.3 | 201.9 | 113.5 |
| | 3.2 | (413.9) | (528.5) |
| | (max. 38.8) | | |

Source: Adapted from Singh, 1976.

[a] All values are in ppt.
[b] This quantity is the mean of the entire sampling period.
[c] This quantity is the standard deviation.

Table 4 summarizes the atmospheric chemistry of those chlorinated hydrocarbons that have been shown to form phosgene in a smog chamber. Phosgene formation is likely to pose a problem only during periods of adverse weather such as an inversion. Perchloroethylene and trichloroethylene have the greatest potential for phosgene formation during such a period due to their short atmospheric half-life.

Table 4. Summary of the Atmospheric Chemistry of Some Demonstrated Phosgene Precursors

| Compound | Estimated atmospheric emissions ($10^6$ lb)[a] | Estimated half-life (years) | Tropospheric chlorinated reaction products |
|---|---|---|---|
| Chloroform | 6 | 0.2 | Phosgene (67%)[b]<br>Chlorine monoxide (33%) |
| Methylene chloride | 418 | 0.3 | Phosgene (100%)<br>(HCl?) |

Table 4. (continued)

| | | | |
|---|---|---|---|
| Perchloroethylene | 617 | 0.01 | Trichloroacetyl chloride (80%)<br>Phosgene (10%)<br>Hydrogen chloride (10%) |
| Trichloroethylene | 417 | 0.001 | Dichloroacetyl chloride (70%)<br>Phosgene (12%)<br>Formyl chloride (8%)<br>Hydrogen chloride (10%) |

Source: EPA, 1975.

[a] 1973 domestic emissions.

[b] Quantity in parentheses represents an approximation of the amount of chlorine from the original compound in each chlorinated reaction product. This column does not account for all products, only those containing chlorine.

It is difficult to assess the magnitude of the problems of phosgene formation in the atmosphere. Phosgene is evidently one of the reaction products of a number of high-volume (both in terms of production and emissions) chlorinated hydrocarbon solvents. However, the role and significance of each solvent, the half-life of phosgene in the air, and the atmospheric fate of phosgene are not well understood. Nevertheless, it is evident from Figure 1 that phosgene and the various chloroacetyl chlorides represent the major tropospheric photooxidation products of chlorinated hydrocarbons.

### Cigarettes

Phosgene is known to form following the exposure of certain chlorinated hydrocarbons to a temperature of 400°C or more. On the basis of this, several investigators in the 1930's suggested, without experimental verification, that phosgene could form either in a smoked cigarette or at its burning tip in the presence of halogenated hydrocarbons.

Elkins and Levine (1939) carried out the first experiments which examined the effluent from cigars and cigarettes smoked in atmospheres containing a number of halogenated hydrocarbon vapors. Among the organic halides tested were trichloroethylene,

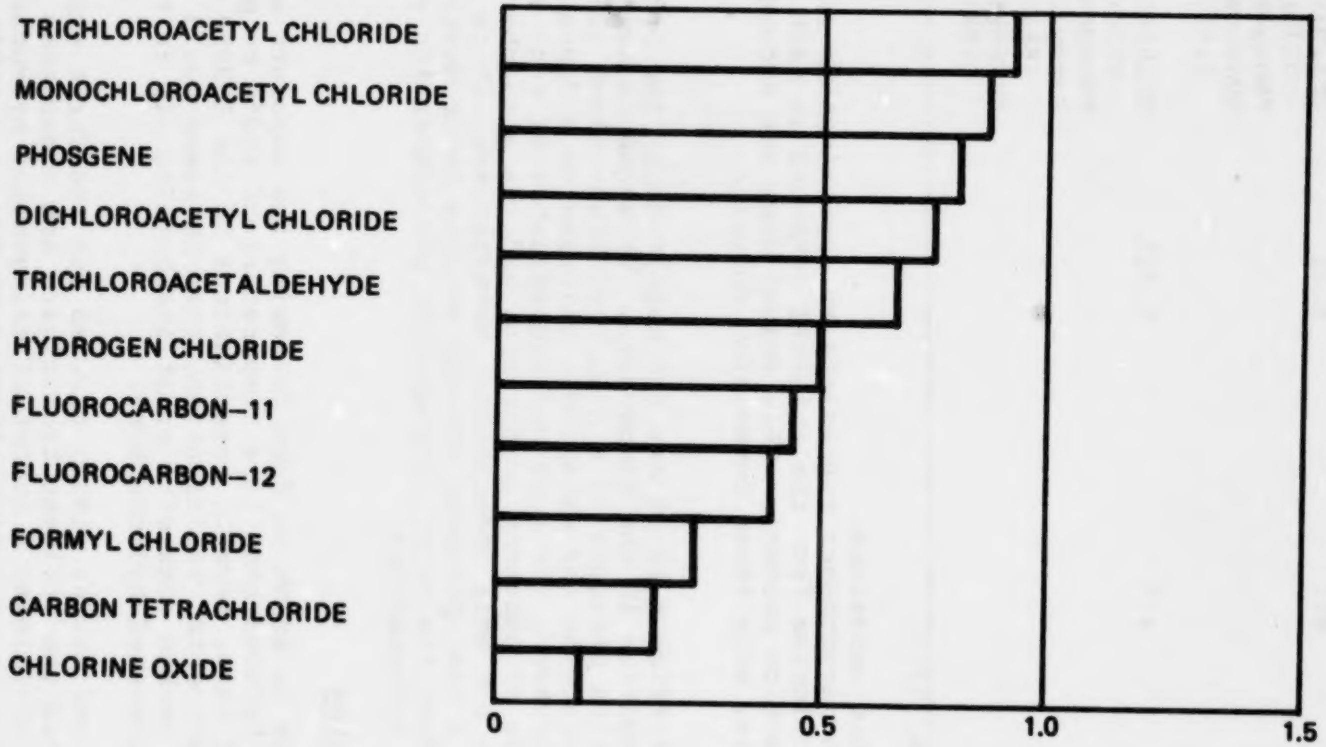


Figure 1. Worldwide amounts of chlorine in halogenated compounds after photooxidation in troposphere and lower stratosphere, 1973. (Source: EPA, 1975.)

carbon tetrachloride, dichlorobenzene, dichlorofluoromethane, ethylene dibromide, and ethyl bromide. The analytical method used did not test the inhaled gases specifically for phosgene, but measured the total halide content of the combustion gases. The amount of halide found in the exit gases, however, was so small that even if all the chloride (or bromide) was present as phosgene, it would "not constitute a health hazard," or so the authors concluded.

Little (1955) conducted a series of experiments which attempted to quantitatively measure the formation of phosgene in or at the tip of a cigarette. The reported limit of detection was 0.05 ppm phosgene (v/v). The results of the experiment are summarized in Table 5. As can be seen, in no instance was phosgene detected at or above 0.1 ppm. Even the addition of phosgene to the experimental atmosphere failed to yield positive results. Little attributed these findings to the absorption of phosgene by tar and other constituents of the combusted cigarette. Tar absorption of phosgene is quite effective, as it was subsequently found that the tar from a single cigarette could effectively keep the phosgene in sampled air below the detection limit for 20 min despite an atmosphere spiked with 50 ppm phosgene and an experimental "smoking" rate of 30 l/hr.

Table 5. Detection of Phosgene in Atmospheres Contaminated with Chlorinated Hydrocarbons (ppm)

| Solvent | Solvent concentration | Phosgene in "inhaled" gases | Phosgene adjacent to cigarette tip | Phosgene above cigarette tip |
|---|---|---|---|---|
| Carbon tetrachloride | 50 | <0.1 | <0.1 | <0.1 |
|  | 2,000 | <0.1 | <0.1 | <0.1 |
| Chloroform | 300 | <0.1 | <0.1 | <0.1 |
|  | 2,000 |  | <0.1 | <0.1 |
| Perchloroethylene | 200 | <0.1 | <0.1 | <0.1 |
|  | 2,000 |  | <0.1 | <0.1 |
| Tetrachloroethane | 10 | <0.1 |  |  |
| Trichloroethylene | 200 | <0.1 | <0.1 | <0.1 |
|  | 2,000 | <0.1 | <0.1 | <0.1 |
| Phosgene | 0.2 | <0.1 |  |  |
| Phosgene | 20 | <0.1 |  |  |

Source: Little, 1955.

A recent study by Hanst et al. (1977) demonstrated that chlorofluoromethanes do not decompose to form toxic products (specifically $COCl_2$, COClF, and $COF_2$) when in the presence of a burning cigarette. The experimental procedure called for mixtures of chlorofluoromethanes and air to be drawn through cigarettes and then into an infrared absorption cell where the spectra would be recorded. The yields of COClF from 2,000 ppm of trichlorofluoromethane (F-11) in air and $COF_2$ from 2,500 ppm of chlorodifluoromethane (F-22) in air were each less than 2 ppm. No phosgene was detected in either case. In addition, the spectra showed that the chlorofluoromethanes were not decomposed in passage through the burning cigarette since the fluorocarbons were identified in the sample "downstream" from the cigarette.

## UV-Induced Formation

A number of solvent degreasers have been shown to react in air to form phosgene in the presence of short-wave (UV) radiation generated by welding arcs. Among the chlorinated hydrocarbons shown to produce phosgene in the described situation are methyl chloroform (Dahlberg et al., 1973), trichloroethylene (Dahlberg and Myrin, 1971; Glass et al., 1971), and perchloroethylene (Andersson et al., 1975). The consensus among the investigators was that while all the solvents presented the potential for phosgene formation, trichloroethylene was the safest because of the high associated production of dichloroacetyl chloride (5:1 ratio in production of dichloroacetyl chloride to phosgene). The reasoning was that dichloroacetyl chloride, a strong lachrymatory agent, would offer adequate warning of the presence of undetectable levels of phosgene. In the case of methyl chloroform, the production of hydrogen chloride (at about 5 times that of phosgene) and trace amounts of acetyl chloride would in combination be unlikely to produce sufficient irritancy to yield an adequate warning of the presence of phosgene. Perchloroethylene was seen as perhaps the most hazardous of the three in this regard because of its rapid decomposition to phosgene (perchloroethylene absorbs radiation most strongly at longer wavelengths where the emission from most welding arcs is very intense). Trichloroacetyl chloride, which could serve as a phosgene warning agent (because of its penetrating, lachrymatory smell), was, however, found to have almost the same rate of production as phosgene and thus would not give adequate notice (Dahlberg and Myrin, 1971; Dahlberg et al., 1973; Andersson et al., 1975).

The problem of UV-induced formation of phosgene appears likely to be of significance only in an occupational context.

## REFERENCES

Andersson, H. F. et al. Phosgene formation in air contaminated with perchlorethylene. Ann. Occup. Hyg. 18(2):129, 1975.

Cameron, G. R. et al. Effect of exposing different animals to a low concentration of phosgene 1: 5,000,000 (0.9 mg/m$^3$) for 5 hours on 5 consecutive days. Chapter VIII in First Report on Phosgene Poisoning, Porton Report No. 2349, Washington, D.C., British Defense Staff, British Embassy, April 29, 1942. (As cited in NIOSH, 1976)

Chemical Economics Handbook (CEH). Menlo Park, Calif., Stanford Research Institute. 1975.

Dahlberg, J. A., and L. M. Myrin. The formation of dichloroacetylchloride and phosgene from trichloroethylene in the atmosphere of welding shops. Ann. Occup. Hyg. 14(3):269, 1971.

Dahlberg, J. A. et al. On the formation of phosgene by photo-oxidation of methyl chloroform in welding. Ann. Occup. Hyg. 16:41, 1973.

Elkins, H. B., and L. Levine. Decomposition of halogenated hydrocarbon vapors by smoking. J. Ind. Hyg. 21:221, 1939.

Gay, Bruce W. Atmospheric oxidation of chlorinated ethylenes. Environ. Sci. Technol. 10(1):58, 1976.

Glass, W. I. et al. Phosgene poisoning: Case report. N. Z. Med. J. 74(475):386, 1971.

Hanst, Philip L. et al. Chlorofluoromethanes: Their thermal stability in passing through cigarettes. U.S. Environmental Protection Agency, ESRL. January 1977.

Hardy, E. E. Phosgene. In Kirk-Othmer Encyclopedia of Chemical Technology. 1964.

Little, J. The formation of phosgene by the action of hot surfaces and its absence when tobacco is smoked in atmospheres containing chlorinated hydrocarbon vapours. Br. J. Ind. Med. 12:304, 1955.

NIOSH. Criteria for a Recommended Standard . . . Occupational Exposure to Phosgene. U.S. DHEW, PHS, CDC, NIOSH, HEW Publ. No. (NIOSH)76-137. 1976.

Patty, F. A. Phosgene. In F. A Patty (ed.), Industrial Hygiene and Toxicology, 2nd ed., vol. 2. New York, John Wiley and Sons. 1963. p. 938-940.

Sax, N. Irving (ed.). Dangerous Properties of Industrial Materials, 3rd ed. New York, Van Nostrand Reinhold Co. 1968.

Singh, H. B. Phosgene in ambient air. Nature 264:428, 1976.

Singh, H. B. et al. Atmospheric formation of carbon tetrachloride from tetrachloroethylene. Environ. Lett. 10(3):253, 1975.

Spence, J. W., P. L. Hanst, and B. W. Gay, Jr. Atmospheric oxidation of methyl chloride, methylene chloride, and chloroform. J. Air Pollut. Control Assoc. 26(10):994-996, 1976.

U.S. Environmental Protection Agency (EPA). Report on the Problems of Halogenated Air Pollutants and Stratospheric Ozone. Publ. No. EPA-600/9-75-008. December 1975. PB-247-699

Winell, M. An international comparison of hygienic standards for chemicals in the work environment. Ambio 4:34, 1975.

# CHEMICAL HAZARD INFORMATION PROFILE

## Sodium Azide

Date of report: August 1, 1977

This chemical was chosen for study because of its proposed use in automobile air bags.

Sodium azide is not recommended for further priority evaluation within OTS at this time. DOT is studying the safety of its proposed use in auto air bags.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

### Chemical Identity

Sodium azide is a stable, neutral, white to colorless crystalline solid. It decomposes at 300 C and is soluble is water and liquid ammonia. When sodium azide is dissolved, hydrazoic acid ($HN_3$) is released from solution (Merck Index, 1969).

### Production and Use

Sodium azide is presently used as an intermediate in organic synthesis (Sutton, 1963) and in the preparation of hydrazoic acid, lead azide, and pure sodium (Merck Index, 1969). It also finds use in fungicidal and nematodicidal compounds, as a preservative in diluents used with automatic blood cell counters, and as a common reagent in hospitals and chemical laboratories (Fishbein, 1977). The estimated domestic production in 1974 is less than 1,000 lb (EPA, 1977).

In June 1977, the Department of Transportation announced that passive restraints would begin to become mandatory on new automobiles in 1983. The system that appears most likely to be the major method of meeting the passive restraint requirements is the so-called air bag. Briefly, the air bag is a device wherein impact of the vehicle causes two bags to be instantaneously inflated to cushion the front seat occupants from the force of the impact. In the most common air bag designs, the bag is inflated by means of a solid prochemical composition which, upon impact, is detonated, forming a gas to inflate the bag. In these designs, there is a large air bag on the passenger side of the vehicle that has perforations to allow the bag to deflate quickly after inflation. A second bag on the driver's side is much smaller and is not perforated.

Of interest here are the solid pyrochemical compositions. The primary component of the compositions now most favored for the air bag is sodium azide ($NaN_3$). This highly toxic substance is currently produced and used in negligible quantities, but its use in the air bag would require large production expansion, greatly increasing the potential environmental and human exposure to it. (Additional information from the patent literature on the use of sodium azide for air bag gas generation is given in the appendix.)

According to Department of Transportation estimates, between 11 and 17 million lb of pyrochemicals will be needed for air bags annually by about 1990. While the exact proportion of sodium azide to be used in the pyrochemical composition is unknown, its production would clearly rise into the millions of pounds per year to meet the air bag use demand.

The liquid ammonia process is the preferred method for the production of sodium azide in the United States. In this method, sodium reacts with liquid ammonia in the presence of a catalyst (such as ferric nitrate) to form sodamide ($NaNH_2$). The slurry of sodamide in liquid ammonia produced in this reaction is then treated with nitrous oxide under pressure to produce the azide. Sodium azide is separated from the caustic mixture by recrystallization from water (Lemke, 1969).

## Health Aspects

Sodium azide is rapidly absorbed from the gastrointestinal tract and from injection sites; however, the effectiveness of its absorption from the lungs and skin has apparently been little studied. Sodium azide is a highly toxic poison for both laboratory animals and man. The symptoms generally observed in animals following acutely lethal dosing are respiratory stimulation and convulsions followed by nervous system depression and death. With lower doses the occurrence of convulsions is variable, but there occurs a consistent, prompt, transient fall in blood pressure. Rabbits exhibit a 40 to 60% decline in blood pressure following oral administration of 3 to 10 mg azide per kg. The hypotensive effect lasts for over 1 hr. At 2 mg/kg, the drop in blood pressure is severe, though of shorter duration. As little as 1 mg/kg intravenously in cats produces hypotension. Hypertensive patients characteristically suffer a greater drop in blood pressure than do normotensive individuals. Doses of 0.01 to 0.02 mg/kg administered orally to humans produce a prompt fall in blood pressure lasting 10 to 15 min (Sutton, 1963).

The following are summaries of the biological effects attributed to sodium azide.

### Mutagenesis

Sodium azide induced a high frequency of mutations with negligible frequencies of chromosome aberrations in barley seeds (Nilan et al., 1973). In another study, sodium azide treatment of barley seeds induced a mutation rate of 10 to 30%. No chromosomal aberrations during the first mitosis were detected in seeds examined immediately after azide treatment or following 12 months of storage (Walther, 1975).

Sodium azide is a potent mutagen of salmon sperm DNA in an acidic environment. The mutagenic activity, however, is not associated with chromosomal aberrations. The mutagenic effect is partially explained on the basis of a base substitution mechanism (Sideris and Argyrakis, 1974).

African violet plants are susceptible to sodium azide-induced mutagenesis (Warfield, 1974).

Sodium azide effectively reverts S. typhimurium strain TA1530, indicating that it is a base substitution mutagen. The chemical is ineffective on strains TA1531, TA1532, and TA1534, which are frameshift mutants (Nilan et al., 1973).

Sodium azide treatment has been shown to slightly increase the frequency of penicillin- and streptomycin-resistant mutants in Staphylococcus aureus (Berger et al., 1953).

Sodium azide alone failed to induce sex-linked recessive lethal mutations in Drosophila melanogaster (Sobels, 1954, 1955). However, when in combination with carbon monoxide, a slight increase in lethal mutations occurred (Clark, 1958).

### Carcinogenesis

A 2-year rat study was conducted to determine the chronic toxicity or carcinogenicity of sodium azide. Apparently the maximal tolerated dose (unspecified) and half that level were given in the diet or by gastric intubation twice weekly to male and female rats for 18 months followed by a 6-month observation period. Under the conditions of the experiment, sodium azide was determined to be noncarcinogenic (Ulland et al., 1973).

### Metabolic Effects

Sodium azide interferes with oxidative enzymes and uncouples oxidative phosphorylation in rat liver mitochondria cells (Zvyagilskaya et al., 1969; Bogucka and Wojtczak, 1966). These actions cause a disruption in energy transfer mechanisms within the cell and thereby inhibit the production of ATP, the principal energy storage molecule.

Mg-ATPase (an ATP-splitting or energy-releasing enzyme) of the mitochondrial fraction of rat brain cells was inhibited by sodium azide (Bigl and Biesold, 1970).

Sodium azide inhibited DNA synthesis and cell division in S. typhimurium (Ciesla et al., 1974). It was also found to inhibit RNA and protein synthesis in ascites ovary carcinoma cells (Stelletskaya et al., 1973).

Sodium azide, through disruption of the energy transfer enzymes, inhibited cilia movement and phagocytosis in Tetrahymena pyriformis (Burmeister, 1974).

### Neurological Effects

Intravenous injections of up to 16 mg of sodium azide per kg produced a rapid drop in blood pressure, followed by convulsions accompanied by unconsciousness, vascular congestion, and apnea (breathing stoppage) in 10 of 11 rhesus monkeys. Cerebellar damage, ranging from the loss of Purkinje cells of the folia lining the depth of the horizontal fissures to almost total decortication (complete removal of the cerebellar lining), was also produced following the acute exposure. Two of the monkeys died, and ataxia or loss of muscular coordination developed in eight of the remaining monkeys. The ataxia, due to cerebellar cortical destruction following sodium azide-induced convulsions, may be attributed to the cumulative effects of impaired ventilation, hypotension, and impaired oxidative enzyme activity (Mettler and Sax, 1972).

Sodium azide has also been implicated in the production of dyskinesia, impairment of the power of voluntary movement, in monkeys (Sassin, 1975).

Daily intramuscular injections of 5 mg sodium azide per kg into monkeys can, if continued over periods of 4 to 5 weeks, produce abnormal movements. Necropsies following sacrifice found basal ganglia necrosis (Hurst, 1942). The same investigator also found that (daily?) intramuscular doses of 6, 7, and 8 mg/kg produced symptoms of poisoning on the 17th, 14th, and 8th days, respectively (Hurst, 1944).

### Acute Human Exposure and Hypotension

A male patient in a hematology lab accidentally drank a solution containing 50 to 60 mg of sodium azide. Within 5 min he collapsed and briefly lost consciousness. The patient complained of nausea, a severe headache, and feeling hot. Gastric washing was performed 10 min following ingestion. After 1 hr, all symptoms had disappeared except for the headache, which lingered until the next morning (Richardson et al., 1975).

A technician in a hematology lab ingested an estimated 5 to 10 mg of sodium azide. She complained of headache, sweating, and faintness within 5 min of exposure. The complaints dissipated shortly thereafter (Richardson et al., 1975)).

In a similar episode, a blood lab technician accidentally ingested what was estimated to be a "very small amount" of sodium azide. Symptoms of tachycardia, hyperventilation, and hypotension were observed. The authors note that the minimal hypotensive dose in humans lies between 0.2-0.4 g/kg (Roberts et al., 1974).

While acidifying 10 g of sodium azide in a malfunctioning laboratory hood, a chemist complained of dizziness, weakness, blurred vision, shortness of breath, and faintness following a few minutes of exposure. The chemist was observed to have bradycardia and a moderate reduction in blood pressure. Recovery was complete in 1 hr (Sutton, 1963). No estimate of the dose received was noted in the report; moreover, there was no conclusive demonstration that the chemist was exposed predominantly to sodium azide, as it appears likely that hydrazoic acid would also be evolved. However, the case was seen as important in that it offered the first demonstration that the effects of respiratory exposure to simple azides were similar to those seen following oral or IV administration.

Several additional citations were located which dealt with acute exposures to sodium azide (Emmett and Ricking, 1975; Kozlicka-Gojdzinska et al., 1966). Unfortunately, not enough information was available in the abstracts to permit a discussion of the findings.

## Environmental Aspects

### Phytotoxic Effects

Sodium azide finds some use in fungicidal and nematodicidal compounds. Because of this use, several investigators have looked into sodium azide's effects on plants. Within the context of the present investigation, the phytotoxic characteristics of sodium azide are of interest with respect to the disposal of the chemical in conjunction with the junking of an automobile.

The dissipation of sodium azide from soil is significantly affected by pH, soil moisture, and relative humidity. Acid soils tend to lose sodium azide more rapidly than do alkaline soils. The degree of leaching and phytotoxicity is not affected by soil pH. Bioassay studies indicate that 10 ppm sodium azide in the soil significantly reduces germination and growth in tested plants. At levels below 10 ppm, germination is often delayed, but normal growth occurs following continued dissipation of sodium azide (Ketchersid and Merkle, 1976).

Sodium azide functions as a metabolic poison in plants as in animals (see "Metabolic Effects"). Sodium azide, however, is not immediately effective on the cells of plant roots. Nevertheless, after passage of a lag time to allow penetration and accumulation of sodium azide in soybean and oat roots (suspended in an aqueous medium), the respiration capacity of the roots begins to be affected. The result is a strong increase in the release of soluble organic substances from the roots. This suggests a direct interaction of sodium azide with the protein components of cellular membranes (Shapovalov, 1974).

Stomatal movement in excised leaves is retarded in the presence of sodium azide. However, stomatal closure is not affected under the same circumstances. The author proposes that sodium azide works indirectly on stomata by initially affecting photosynthetic processes (Permadasa, 1974).

## Environmental Chemistry

Sodium azide is stable in water in the absence of light but appears to be susceptible to photodecomposition by solar radiation. Photolysis of sodium azide may result in metal nitrides initially, with the eventual formation of the free metal and nitrogen gas (EPA, 1977).

## APPENDIX. Sodium Azide in Gas Generation

Propellants for automobile air bag inflation are comprised of fine, solid, inorganic reducing and oxidizing agents in intimate mixtures. The agents are compacted without binders or solvents and when combusted produce gases within milliseconds without the generation of explosive force. Possible reducing agents are salts of $NH_2NH_2$, $HN_3$, or $NH_2OH$, while the possible oxidizing agents are salts of $HNO_3$, $HNO_2$, $HClO_4$. The combustion products are identified as $N_2$, $O_2$, and $H_2O$, but no CO or $CO_2$. Thus, saturated solutions of $NaN_3$ and $NH_4ClO_4$ are sprayed into a vacuum chamber, the water is evaporated, and the resulting crystals are collected and compressed into capsules. When combusted, the product produces a gas identified as containing (in mole percent) 67% $N_2$, 37% $O_2$, 1.7% $N_2O$, 2.5% $H_2O$, and 0.0% $NH_3$. A pressure of 1.458 psi is exerted within 0.26 sec (Klager and Dekker, 1974).

A proposed gas-generating agent is composed of a mixture of alkali metal azide or an alkaline earth metal azide and an equivalent amount of $NH_4ClO$ or $NH_4Cl$ mixed with an oxidizing agent. Thus, 67 g of $NaN_3$ is mixed (following combination with a styrene-butadiene copolymer) with 118 g of $NH_4ClO_4$ to produce the gas-generating agent. The mixture is divided into four portions and each is placed in a polyethylene bag (which was previously charged with lead thiocyanate and $KClO_4$). The filled bag is put into a cylindrical gas generator, then into a 70-liter bag, and ignited. A pressure of 1.2 $kg/cm^2$ is generated within 31.2 msec and reaches a maximum of 1.61 $kg/cm^2$, which is maintained for approximately 80 msec (Shiga et al., 1974).

# REFERENCES

Berger, H. et al. Effect of sodium azide on radiation damage and photoreactivation. J. Bacteriol. 65:538, 1953.

Bigl, V., and D. Biesold. Isolation of subcellular particle fractions from brain tissue and distribution of ATP-splitting enzyme. Acta Biol. Med. Ger. 25(1):1, 1970. (Abstract)

Bogucka, K., and L. Wojtczak. Effect of sodium azide on oxidation and phosphorylation processes in rat-liver mitochondria. Biochim. Biophys. Acta 122:381, 1966.

Burmeister, J. Action of enzyme poisons on phagocytosis ability, cilia movement, and metabolism of Tetrahymena pyriformis. Z. Allg. Mikrobiol. 14(6): 479, 1974. (Abstract)

Ciesla, Z., K. Mardarowicz, and T. Klopotowski. Inhibition of DNA synthesis and cell division in Salmonella typhimurium by azide. Mol. Gen Genet. 135(4):339-348, 1974.

Clark, A. M. Genetic effects of carbon monoxide, cyanide and azide on Drosophila. Nature 181:500, 1958.

Emmett, E. A., and J. A. Ricking. Fatal self-administration of sodium azide. Ann. Intern. Med. 83(2):224, 1975. (Abstract)

Fishbein, Lawrence. Potential industrial carcinogens and mutagens. May 1977. (Draft)

Harada, I. et al. Gas-generating agent for inflating protective bags for passengers in case of automobile accidents. Japan Kokai 74(10):887, 1972; Chem. Abstr. 81:39546E, 1974.

Hurst, E. W. Experimental demyelination of the CNS. I. Poisoning with potassium cyanide, sodium azide, hydroxylamine, narcotics, carbon monoxide, etc., with some consideration of the bilateral necrosis occurring in the basal nuclei. Aust. J. Exp. Biol. Med. Sci. 20:297, 1942. (As cited in Mettler, 1974)

Hurst, E. W. Brain 67:103, 1944. (As cited in Mettler, 1974)

Ketchersid, M. L., and M. G. Merkle. Dissipation and phototoxicity of sodium azide in soil. Weed Sci. 24(3):312, 1976. (Abstract)

Klager, K., and A. O. Dekker. Non-toxic gas generation. U.S. Patent 3,814,694, June 4, 1974. Chem. Abstr. 81:172482X, 1974.

Kozlicka-Gojdzinska, H. et al. A case of fatal intoxication with sodium azide. Arch. Toxikol. 22(3): 160, 1966.

Lemke, Charles H. Sodium. In Kirk-Othmer Encyclopedia of Chemical Technology, vol. 18. 1969. p. 432.

The Merck Index, 8th ed. Rahway, N.J., Merck and Co. 1969.

Mettler, F. A. Neuropathological effects of sodium azide administration in primates. Fed. Proc. 31(5):1504, 1974.

Mettler, F. A., and D. S. Sax. Cerebellar cortical degeneration due to acute azide poisoning. Brain 95(Pt. 3):505, 1972. (Abstract)

Nilan, R. A. et al. Azide--A potent mutagen. Mutat. Res. 17:142, 1973. (Abstract)

Permadasa, M. A. Stomatal movements in excised leaves. Effects of sodium azide. New Phytol. 73(4):689, 1974. (Abstract)

Richardson, S. G. N. et al. Two cases of sodium azide poisoning by accidental ingestion of Isoton. J. Clin. Pathol. 28:350, 1975.

Roberts, R. J. et al. Accidental exposures to sodium azide. Am. J. Clin. Pathol. 61(6):879, 1974.

Sassin, J. F. Drug induced dyskinesia in monkeys. Adv. Neurol. 10:47, 1975. (Abstract)

Shapovalov, A. A. Kinetics of the release of water-soluble organic compounds from the cells of plant roots induced by urea and sodium azide. Fiziol. Rast. 21(6):1243, 1974. (Abstract)

Shiga, M. et al. Generating gases for inflating protective bags for passengers in case of automobile accidents. Jpn. Kokai 74(10):895, 1974. (Abstract)

Sideris, E. G., and M. Argyrakis. Chemical alterations induced in DNA and DNA components by the mutagenic agent azide. Biochim. Biophys. Acta 366(4):367, 1974. (Abstract)

Sobels, F. H. The effect of pretreatment with cyanide and azide on the rate of x-ray induced mutations in Drosophila. Z. Vererbungsl. 86:399, 1955.

Sobels, F. H. The influence of catalase inhibitors on the rate of x-ray induced mutations in *Drosophila melanogaster*. Proc. 1st Int. Photobiol. Congr. Amsterdam. 1954. p. 332.

Stelletskaya, N. V. et al. Metabolism of RNA in the presence of inhibitors of energy metabolism. Biokhimiya 38(6):1267, 1973. (Abstract)

Sutton, William L. Heterocyclic and miscellaneous nitrogen compounds. *In* F. A. Patty (ed.), Industrial Hygiene and Toxicology, 2nd ed., vol. II. New York, John Wiley and Sons. 1963. p. 2208-2211.

Ulland, B. et al. Chronic toxicity and carcinogenicity of industrial chemicals and pesticides. Toxicol. Appl. Pharmacol. 25(3):446, 1973. (Meeting abstract)

U.S. Environmental Protection Agency (EPA). Review of the Environmental Fate of Selected Chemicals. Publ. No. EPA-560/5-77-003. May 1977.

Walther, F. The influence of storage on sodium azide treated barley seeds and on the efficiency of the chemomutagen. In: Proceedings of the International Barley Genetics Symposium. 1975. p. 123-131.

Warfield, D. L. Azide mutagenicity and peroxidase inhibition. Mutat. Res. 23:399, 1974. (Abstract)

Zvyagilskaya, R. A. et al. Accumulation of azide in mitochondria and the effect of azide on energy metabolism. Acta Bioshim. Pol. 16(2), 1969. (Abstract)

# CHEMICAL HAZARD INFORMATION PROFILE

## Styrene Oxide

Date of report: March 9, 1978

This chemical was chosen for study because it has a relatively high production volume and because it is a presumed metabolite of styrene, a very high-volume chemical.

The following recommendations are made regarding further OTE evaluation of the possible health or environmental hazards of styrene oxide:

(1) Require TSCA Section 8(a) submission--Little information is available on the production and uses of styrene oxide.

(2) Require TSCA Section 8(d) submissions--Information on chronic toxicity is limited.

(3) Consider need for testing--Styrene oxide is a presumed metabolite of styrene. If so, there could be extensive exposure to styrene oxide. Styrene oxide is mutagenic in several in vitro systems.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

## Chemical Identity

Styrene oxide ($C_6H_5\overline{CHCH_2O}$) is a colorless to pale straw-colored liquid. It boils at 194.2°C (760 mm Hg) and freezes at -36.7°C. Synonyms for styrene oxide (CAS No. 96-09-3) include phenylethylene oxide, phenyl oxirane, 1-phenyl-1,2-epoxyethane, and 1,2-epoxyethylbenzene. The density of styrene oxide is 1.0540 at 20°C. It is completely soluble in acetone, benzene, carbon tetrachloride, ethyl ether, heptane, and methanol (Standen, 1965). Styrene oxide is miscible with water (0.28% at 25°C). Styrene oxide is a moderate fire hazard when exposed to heat or flames. When heated it emits acrid fumes, and it can react with oxidizing materials (Sax, 1968).

## Production and Use

Styrene oxide is made commercially from styrene via the intermediate chlorohydrin. Styrene oxide could also be prepared commercially by epoxidation of styrene with peroxyacetic acid. It is used as a reactive intermediate, especially to produce styrene glycol and its derivatives. Substantial amounts are also used in the epoxy resin industry as a diluent (Patty, 1963). It may also have applications in the preparation of agricultural and biological chemicals, cosmetics, and surface coatings and in the treatment of textiles and fibers (IARC, 1976).

Styrene oxide is produced by Union Carbide Corp. in Taft, La., and Texas City, Tex. (SRI, 1975). It is estimated that 1 to 2 million lb of styrene oxide is produced annually (SRI, 1977).

## Health Aspects

Acute human exposure to styrene oxide causes skin irritation. Some evidence suggests that styrene oxide is absorbed slowly through the skin. Styrene oxide is a presumed metabolite of styrene. Investigations have shown that the ultimate excretion product in many animals is hippuric acid. Urine of workers exposed to styrene oxide vapor contained large amounts of mandelic acid and phenylglyoxylic acid (both compounds in the proposed metabolic pathway of styrene oxide), but the hippuric acid concentrations were normal (IARC, 1976).

The $LD_{50}$ for oral administration of styrene oxide to rats is 4,290 mg/kg. The $LDL_9$ resulting from 4-hr inhalation studies on rats is 500 ppm, while the $LC_{50}$ is 1,000 ppm. The $LD_{50}$ for styrene oxide by skin application in male New Zealand rabbits is 1,060 mg/kg. It causes corneal injury in rabbits even at dilutions of 1%. The $LD_{50}$ for rats for intraperitoneal injection of styrene oxide is 460 mg/kg (IARC, 1976; NIOSH, 1976).

No tumors were observed in those mice which survived (33/40) for 17 to 24 months, during which time they were painted three times a week with a 5% solution of styrene oxide in acetone. Of a similar group of 40 mice painted with a 10% solution, only 2 survived to 17 months; neither showed tumors. This study was designed to screen a large number of epoxides. No information on a control group or the tumor incidence in a control group was given (Weil et al., 1963).

Of 30 male mice given thrice-weekly dermal application of 0.1 ml of a 10% solution of styrene oxide in benzene, three developed skin tumors, and one of these had a squamous cell carcinoma. Of 150 benzene-painted controls, 11 developed skin tumors, and one of these had a squamous cell carcinoma. The IARC concluded that no significant increase in skin tumors occurred (IARC, 1976; NIOSH, 1976).

Styrene oxide induced mutations in strains of Salmonella typhimurium sensitive to mutagens causing base-pair substitution. Other styrene metabolites were found nonmutagenic in this study (Milvy, 1976). Styrene has also been shown to be mutagenic to such strains, but only after metabolic activation (Vainio et al., 1976). Styrene oxide caused forward mutations in Chinese hamster cells, as well as in yeast, and was mutagenic in a mitotic gene conversion system of yeast (Luprieno, 1976).

## Environmental Aspects

No information on the environmental aspects of styrene oxide was found.

## REFERENCES

Hawley, Gessner G. (ed.). Condensed Chemical Dictionary, 9th ed. New York, Van Nostrand Reinhold Co. 1977.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, vol. 11. 1976.

Luprieno, N.A. et al. Mutagenicity of industrial compounds: Styrene and its possible metabolite styrene oxide. Mutat. Res. 40(4):317-24, 1976.

Milvy, P. Mutagenic activity of styrene oxide (1,2-epoxyethylbenzene), a presumed styrene metabolite. Mutat. Res. 40(1):15-18, 1976.

NIOSH. Registry of Toxic Effects of Chemical Substances, 1976 ed.

Patty, Frank A. (ed.). Industrial Hygiene and Toxicology, 2nd ed., vol. II. New York, John Wiley & Sons, Inc. 1963. p. 1649-1651.

Sax, N. Irving (ed.). Dangerous Properties of Industrial Materials. New York, Van Nostrand Reinhold Co. 1968.

SRI (Stanford Research Institute). Directory of Chemical Producers. Menlo Park, Calif. 1975.

SRI. Chemical Economics Handbook. Menlo Park, Calif. 1977.

Standen, Anthony (exec. ed.). Kirk-Othmer Encyclopedia of Chemical Technology, 2nd ed., vol. 8. New York, John Wiley & Sons, Inc. 1965. p. 289.

Vainio, H. et al. A study on the mutagenic activity of styrene and styrene oxide. Scand. J. Work Environ. Health 2(3):147-51, 1976.

Weil, Carrol S. et al. Experimental carcinogenicity and acute toxicity of representative epoxides. Am. Ind. Hyg. Assoc. J. 24:305-324, 1963.

# CHEMICAL HAZARD INFORMATION PROFILE

## Sulfur Hexafluoride

Date of report: July 10, 1978

This chemical was chosen for study because of reports that it is contaminated with more toxic sulfur compounds, such as $S_2F_{10}$.

The following recommendations are made regarding further OTE evaluation of the possible health or environmental hazards of sulfur hexafluoride ($SF_6$):

(1) Defer judgment until additional information is obtained from a contractor literature search--Current information is insufficient for judgment.

(2) Request information on composition and purity from manufacturers--Since $SF_6$ itself is a relatively inert compound, a major concern is the possible presence of much more toxic impurities.

(3) Update this CHIP based on the additional information obtained.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

### Chemical Identity

Synonyms: Sulfur fluoride, elegas

CAS No.: 551-62-4

Sulfur hexafluoride ($SF_6$) is a colorless, odorless gas. It has a latent heat of fusion of -50.5°C and a latent heat of sublimation of 63.8°C (Braker and Mossman, 1971). $SF_6$ is slightly soluble in water and soluble in alcohol and ether. It is incombustible (ITII, 1976).

## Production and Use

$SF_6$ is manufactured by passing fluorine over coarse sulfur, followed by several purification steps (Braker and Mossman, 1971). It can be produced by direct fluorination of sulfur or from sulfur dioxide and fluorine. Major decomposition products of $SF_6$ include hydrogen fluoride (Mazella, 1978), sulfuryl fluoride, and thionyl fluoride (Sax, 1968).

Two companies are known to be producing $SF_6$, Allied Chemical and Air Products and Chemicals (Mazella, 1978).

There are no production figures available, although a spokesman from Allied Chemicals estimated that production volume centered around 1 million lb per year. The spokesman also stated that Allied Chemical is responsible for the bulk of the production volume (Mazella, 1978).

$SF_6$ is used in various electric power applications as a gaseous dielectric or insulator. The most extensive use is in high-voltage transformers. $SF_6$ is also used in circuit breakers, waveguides, linear particle accelerators, Van de Graaff generators, chemically pumped continuous-wave lasers, transmission lines, and power distribution substations (Mazella, 1978).

Nonelectrical applications include use as a protective atmosphere for casting of magnesium alloys and use as a leak detector or in tracing moving air masses (Mazella, 1978).

Several sources note that vitreous substitution of $SF_6$ in owl monkeys results in a greater ocular vascular permeability than that caused by saline. This implies that $SF_6$ could have an important use in retinal surgery (Constable and Swann, 1975; Fineberg et al., 1975).

### Production and Use of Major Decomposition Products

In 1973, 365,000 short tons of hydrogen fluoride (HF) was consumed by the United States for a variety of purposes. Major applications include use in production of fluorocarbons, in production of chemicals involved in aluminum smelting and separation of U-235 and U-238, and as a gasoline alkylation catalyst (CEH, 1976).

$SO_2F_2$ is used mainly as an insecticide and fumigant (Vikane ). Domestic consumption of $SO_2F_2$ in this application was 0.9 million lb in 1975. $SO_2F_2$ is also used in organic synthesis and in medicine and dyestuffs. Production figures for these applications are lacking (CEH, 1976).

Information on production of $SO_1F_2$ is at a minimum. This chemical is not listed in the Chemical Week Buyers' Guide Issue, indicating that it is not produced in marketable quantities. Use information for this chemical is lacking.

## Health Aspects

### Sulfur Hexafluoride

$SF_6$ is considered to be physiologically inert in the pure state. It can be absorbed into the body by inhalation, by ingestion, or through the skin. Only slight effects result, regardless of the amount absorbed or the extent of exposure. In high concentrations, however, pure $SF_6$ can act as a simple asphyxiant by displacing the necessary oxygen (Sax, 1968).

Major Decomposition Products. Ordinarily $SF_6$ does not exist in the pure state. It contains variable quantities of sulfur fluorides. In the presence of water, these sulfur fluorides can hydrolyze to yield hydrogen fluoride (HF) and oxyfluoride compounds such as sulfuryl fluoride ($SO_2F_2$) and thionyl fluoride ($SOF_2$) (Mazella, 1978). These compounds have much more toxic health effects.

HF is a toxic, colorless gas with a sharp, penetrating odor. Vapors and liquid can cause damage to the skin, resulting in slowly healing sores. The subcutaneous tissues may also be affected, becoming blanched and bloodless. Gangrene of the affected areas may result (Sax, 1968).

Inhalation of vapor of HF leads to constricted breathing, coughing, and irritation of the throat. Ulceration of the upper respiratory tract or chemical pneumonia may follow (Braker and Mossman, 1971).

Vapors and liquid HF are very dangerous when in contact with the eyes (Braker and Mossman, 1971).

$SO_2F_2$ is a toxic, colorless gas. High concentrations of this gas may result in narcotic action. Accidental exposure of a human worker caused nausea, vomiting, cramps, and itching (Sax, 1968).

Truhaut et al. exposed rats, mice, and rabbits to atmosphere containing lethal doses of $SO_2F_2$ for 60-240 min. They found that $SO_2F_2$ is a convulsant. Most animals died from asphyxia because respiratory muscles were blocked by convulsive crisis (Truhaut et al., 1973).

Truhaut et al. also exposed rats, mice, and rabbits to atmosphere containing lethal doses of $SOF_2$ for 60-240 min. They reported that $SOF_2$ is a pulmonary irritant which induces acute edema. The exposed animals died of asphyxia (Truhaut et al., 1973).

## Environmental Aspects

### Sulfur Hexafluoride

$SF_6$ is chemically inert in its pure state and does not pose an immediate threat to the environment (Sax, 1968). $SF_6$ has an atmospheric half-life of 1-3 years (Krey et al., 1976).

Major Decomposition Products. $SF_6$ generally occurs in an impure form, containing variable quantities of sulfur fluorides. Some of these sulfur fluorides can be highly corrosive. Hydrolysis products of sulfur fluorides (HF, $SO_2F_2$, $SOF_2$) are also highly corrosive (Sax, 1968).

## REFERENCES

Braker, W., and A. L. Mossman. Matheson Gas Data Book, 5th ed. East Rutherford, N.J., Matheson Gas Products. 1971. p. 521-523.

Chemical Economics Handbook (CEH). Menlo Park, Calif., Stanford Research Institute. July 1976.

Chemical Week Buyers' Guide Issue. 1977.

Constable, I. J., and D. A. Swann. Vitreous substitution with gases. Arch. Ophthalmol. 93(6):416-419, 1975.

Fineberg, E. et al. Sulfur hexafluoride in owl monkey vitreous cavity. Am. J. Ophthalmol. 79(1):67-76, 1975.

International Technical Information Institute (ITII). Toxic and Hazardous Industrial Chemicals Safety Manual. Tokyo. 1976.

Krey, P. W. et al. Atmospheric residence of sulfur hexafluoride. U.S. Energy Res. Dev. Admin. April 1976. p. 50-57.

Mazella, Angela (program manager). Production and Use of Sulfur Hexafluoride. Contract No. EPA-68-01-3899. May 31, 1978.

Sax, I. N. (ed.). Dangerous Properties of Industrial Materials, 3rd ed. New York, Van Nostrand Reinhold Co. 1968. p. 1129.

Truhaut, R. et al. Toxicity of some gaseous fluoride and oxyfluoride compounds of sulfur. Arch. Mal. Prof. Med. Trav. Secur. Soc. 34(10-11):581-591, 1973.

# CHEMICAL HAZARD INFORMATION PROFILE

## Tetrahydrofuran

Date of report: October 21, 1977
Revised : November 5, 1979

This chemical was chosen for study because of the high-exposure potential associated with its use as a solvent.

It is recommended that tetrahydrofuran be considered for testing. The NTP Chemical Nomination and Selection Committee has recommended tetrahydrofuran for testing with a medium priority.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

### Chemical Identity

Tetrahydrofuran (THF) also known as 1,4-epoxybutane, tetramethylene oxide, and diethylene oxide is a colorless liquid with an ether-like odor and pungent taste (JRB, 1979). THF imports a characteristic odor to water at or above its olfactory threshold of 3 mg/l. It boils at 66°C and melts at -108.5°C. THF is a saturated cyclic ether possessing good solvent properties for high-molecular-weight polyvinyl chloride, polyvinylidene chloride, and other organic materials. It is miscible with most organic solvents as well as with water in all proportions. Mixtures of THF and water often exhibit better solvent characteristics with certain solutes than one or the other alone. THF is highly flammable and poses a dangerous fire risk. The flash point of THF is 17°C. THF also forms peroxides readily, and thus, has explosive potential (Dunlap, 1967; Condensed Chemical Dictionary, 1977).

### Production and Use

THF is currently manufactured in the US by GAF Corporation, Chemical Products Division and by E.I. Dupont de Nemours and Company, in La Porte, Texas, where it is produced at approximately 90 million pounds per year. Quaker Oats Company, Chemical Division, in Memphis, Tennessee, also manufactures THF at an estimated annual rate of 15 million pounds (JRB, 1979; SRI, 1978). Imports through principal U.S. customs districts are reported as (lbs/yr):

| 1974 | 1975 | 1976 | 1977 |
|---|---|---|---|
| $4.2 \times 10^5$ | $8.2 \times 10^4$ | No data | No data |

Source: U.S. ITC, 1974-1977.

The furfural-based process used by Quaker Oats Co. involves the decarboxylation of furfural to furan in the presence of steam and a zinc-chromium-molybdenum catalyst followed by catalytic hydrogenation to THF. Approximately eight million pounds of THF were produced from furfural in 1973.

The second process reacts acetylene and formalydehyde under high pressure in the presence of a copper catalyst to form butynediol, which is subsequently hydrogenated to butanediol. THF is produced via the dehydration of butanediol. The yield of THF from formaldehyde is about 85% of the theoretical compared to 75% of the theoretical from furfural.

Consumption of formaldehyde-based THF was estimated to have increased at an annual rate of 30% from 26 million pounds in 1969 to 74 million pounds in 1973. Most of the THF produced from furfural is used captively in the manufacture of polytetramethylene glycol (a polyether glycol) which can be used in the production of spandex fibers, polyurethane elastomers, and elastic polyesters. This use represented about 10% of the total estimated THF consumption in 1973. From 1973 through 1978, the consumption of formaldehyde-based THF was expected to grow at an annual rate of 7%, while furfural-based THF consumption was anticipated to remain essentially static over the period (CEH, 1974, 1975). See Table 1 for a summary of domestic consumption figures for THF.

Table 1. Annual Domestic Tetrahydrofuran Consumption (millions of lb/year)

| Year | Consumption |
|---|---|
| 1973 | 82 |
| 1975 | 90 |

Source: CEH, 1975; MITRE Corp., 1976.

THF serves as an intermediate in the preparation of numerous organic chemicals, and is the starting material for the following compounds (JRB, 1979): tetramethylene chlorohydrin; 4-chlorobutylbenzoate; 1,4-diiodobutane; and 4,4-dichlorodibutyl ether.

THF is used as a solvent for high-molecular polyvinyl chloride and polyvinylidene chloride during the preparation of printing inks, adhesives, lacquers, and coating compounds. THF has been widely used as a solvent in the manufacture of steroids.

A large market for THF is its use as a solvent in the Grignard reaction-based production of tetraethyl and tetramethyl lead by the Nalco Chemical Company of Freeport, Texas (CEH, 1975).

One industry source has estimated that approximately 40% of THF consumption is in resin and other solvent applications, 20% as a Grignard reaction solvent, and the remaining 40% as a chemical intermediate (CEH, 1977).

THF is regulated as an indirect food additive. As an adjuvant and production aid, THF may be used as a solvent in the coating of film intended for packaging, transporting, or storing foods, not to exceed 1.5% by weight of film. THF may be used in the base sheet and coating of cellophane used for packaging food, not to exceed a residue limit of 0.17% by weight of finished packaged cellophane. It may also be used as an adjuvant substance in the preparation of resinous and polymeric coatings for polyolefin films used as the food contact surface of articles intended for use in a wide variety of processes involving food (NCI, 1979).

## Health Aspects

### Human Exposure

NIOSH estimates that 90,000 workers in 3,000 plants are exposed to THF. The major industries exposed to THF are special trade contractors and allied products, electric, gas, and sanitary services. The major occupations with potential for exposure to THF are electricians, agriculture and biological technicians, electric linemen and cablemen (NCI, 1979).

Stoughton and Robbins (1936) reported that operators engaged in animal studies with THF suffered from severe occipital headaches after each experiment (as cited by Browning, 1965).

No toxic effects from industrial exposure to THF are noted in the literature. On the basis of animal studies, THF is likely to be somewhat narcotic in man at high concentrations (Browning, 1965).

The adopted TLV-TWA for THF is 200 ppm (590 mg/m$^3$), and the TLV-STEL (threshold limit value-short term exposure limit) is 250 ppm (700 mg/m$^3$) (ACGIH, 1976).

No epidemiological studies or case reports examining the relationship between exposure to THF and human cancer incidences have been found in the literature (NCI, 1979).

### Animal-Chronic Effects

Inhalation of THF at a concentration of 200 ppm daily for 6 hours over a period of 3 weeks caused only a fall in the blood pressure of dogs (Zapp, 1957, as cited by Browning, 1965). Subsequent work by Zapp (1971) as cited by ACGIH (1971) showed that

200 ppm THF in daily, 6-hour exposures produced an observable effect on the pulse pressure of dogs within 3 or 4 weeks. However, continued exposure to 200 ppm THF for a total of 9 weeks followed by 3 weeks of exposure to nearly 400 ppm produced no demonstrable histopathologic changes in the critical organs of the test population.

Using a much higher dosage of 3,400 ppm daily for 20 days, Lehmann and Flury (1943) observed severe irritation of the mucous membranes of rats (as cited by Browning, 1965). One died after three exposures, and two more cats died after six exposures. In contrast to Lehmann and Flury, Zapp (1971) found THF to be neither a skin irritant nor a skin sensitizer. The ACGIH (1971) placed greater reliance on the conclusions of Zapp because of the larger test population.

Repeated (oral?) exposure to 40, 100, and 200 mg/kg of THF for an unspecified amount of time produced "marked cumulative" changes in white mice. Mice receiving the 100-mg/kg dose developed moderate weight loss, paralysis of the hind limbs, leukocytosis, decrease and then an increase in oxygen consumption, and changes in the activity of prothrombin (a blood-clotting factor). The post mortem revealed marked hyperemia of the viscera and protein dystrophy of the liver. A 5- to 6-month experiment conducted on mice, rats, and rabbits revealed similar changes following daily (oral?) administration of 20 mg/kg of THF. In addition, this dose raised the reticulocyte count, reduced cholinesterase activity, and lowered the glycogen content in the liver. A dose of 10 mg/kg, similarly administered, caused mice to lag in their growth. The long-term administration of 5 mg/kg of THF was without detrimental effects (Pozdnyakova, 1969).

In a study by Muller and Reichert in 1969, as cited by NCI (1969) 25 mice received topical applications of 0.1 ml of THF twice weekly for 25 weeks. After 17.5 months, a total of four unspecified benign organ tumors were observed. This experiment may be inadequate for assessment of the carcinogenicity of THF because of the lack of data on controls and inadequate reporting of results.

## Animal-Acute Effects

The minimum lethal dose of THF for rabbits by oral administration is 2.5 g/kg of a 20% solution. The lethal dose in mice by inhalation is 6.7 volume percent in 30 minutes and 4.9 volume percent in 51 minutes. A THF concentration of 2.2 volume percent killed 50% of the exposed mice in 109 minutes. The narcotic dose of THF by inhalation is, for mice, 6.7 volume percent in 5 minutes and 1.1 volume percent in 43 minutes; for dogs, 5.6 volume percent proves narcotic in 2 hours (Stoughton and Robbins, 1936, as cited by Browning, 1965).

The $LD_{50}$ (route unknown) of THF was determined to be 2.3 g/kg for mice, 3 g/kg for rats, and 2.3 g/kg for guinea pigs. Tetrahydrofuran was also somewhat narcotic (Pozdnyakova, 1969).

The acute oral $LD_{50}$ of tetrahydrofuran in three age groups of rats was found essentially the same for all age groups (refer to Table 2 for a summary of results). Tetrahydrofuran was one of the more toxic of the 16 common solvents tested in this investigation (Kirmura et al., 1971).

Acute oral $LD_{50}$ of tetrahydrofuran to three different age groups of rats resulted in the following values: (a = 95% confidence limit) 14 days old, 2.3 (1.4-3.8)$^a$; young adult, 3.6 (3.0 - 4.5)$^a$; and older adult, 3.2 (2.6 - 4.0)$^a$ (Kimura et al., 1971).

Tetrahydrofuran failed to produce evidence of liver damage following the IP administration of 500 mg/kg to mature guinea pigs. Of the four tested animals, one died following the single injection of THF (DiVencenzo and Krasavage, 1974).

The claims of some investigators (Lehmann and Flury in 1943 and Jochmann in 1962, as cited by ACGIH, 1971; Pozdnyakova, 1969) that oral administration of THF caused kidney, liver, and/or lung damage in exposed rats have generally not been substantiated by other workers, although the number of studies is fairly limited (Browning, 1965; Gleason et al., 1969). It is possible that the presence of peroxides, a common impurity of tetrahydrofuran, was responsible in part for these toxic effects not observed by other investigators (Hoffman and Oettel in 1954, as cited by ACGIH, 1971).

### Mutagenicity

No relevant mutagenicity or other in vitro tests on THF were found in the literature (NCI, 1979).

## Environmental Aspects

MITRE Corporation (1976) estimates that approximately 70% of all THF produced annually in the U.S. is ultimately lost to the environment during production and predominantly consumption. It has been detected in a large number of water samples including: effluent discharge from chemical manufacturing plants (in Indiana, several cities in Kentucky, and in the Pacolet and Enoree Rivers in South Carolina), sewage treatment plants (North Carolina), wood preserving plants (Mississippi) and raw sewage (Schackelford and Keith, 1976). THF was also detected in air 500 meters from a factory manufacturing furans and identified as a volatile component of coffee (NIC, 1979).

THF in the atmosphere is expected to form reactive peroxides to an unknown degree (MITRE, 1976).

A Russian investigator, Popov (1971), established that THF may participate in photochemical atmospheric reactions induced by UV irradiation (based on laboratory studies). Tetrahydrofuran, as opposed to other photochemical reactants, yielded few oxidants following irradiation. Nevertheless, the cyclic ether's activity was confirmed by the fairly high conversion rate of nitrogen oxide to nitrogen dioxide associated with tetrahydrofuran. This was true despite tetrahydrofuran's generally low degree of reactivity (compared with other tested organics) as evidenced by the smooth $NO_2$ generation curve identified with THF in Figure 1. The products of the photochemical reactions between THF and nitrogen oxide include aldehydes, acrolein, and formaldehyde. Aldehydes were produced in somewhat higher quantities. The formation of acrolein and formaldehyde from THF was observed to occur considerably later in time than was evident in reactions involving more reactive organic compounds such as heptene (refer to Figure 2).

It will also autooxidize in the presence of light and an excess of atmospheric oxygen to form resinous products which will color water variously from pink to brown. This coloring effect, however, occurs only with relatively high concentrations of THF (100-250 mg/l) (Pozdnyakova, 1969).

Tetrahydrofuran was detected in distilled water for 1 to 2, 6 to 8, and 10 days, respectively, when the initial concentration of THF was 0.5, 5, and 10 mg/l. In the presence of microbial contamination the degradation of THF took 2-3 days less. Thus, THF may be regarded as a fairly stable compound in water. In addition, the chemical and biochemical oxidation of THF is accompanied by considerable consumption of dissolved oxygen contained in the water (Pozdnyakova, 1969).

Experiments with saprophytic microflora demonstrated that THF degrades in water to form hydroperoxides among its various transformation products. One mg of THF produced 1.5 mg of peroxide compounds, while 2.5 mg of THF produced 3.75 mg of such products. The formation of hydroperoxides at these concentrations may be sufficient to exert a bactericidal effect. However, THF at or below 0.5 mg/l was biochemically oxidized with very little hydroperoxide formation. Thus, the presence of THF in concentrations exceeding 0.5 mg/l may disturb the process of natural self-purification occurring in water bodies because of THF's intensive oxygen consumption and the bactericidal properties of the hydroperoxide by-product. The Russian author, on the basis of the preceding, suggested a maximum permissible THF concentration of 5 mg/l in water (Pozndyakova, 1969). (The significance of the preceding article is difficult to assess because of the empirical nature of the presentation. The author fails to discuss the experimental method as well as the conditions of each experiment. Thus, such parameters as temperature, pH, presence of light, the use of open versus closed flasks, etc., are not noted. Nonetheless, the concentration of THF required to produce the reported effects is fairly high (minimum of 170 ppm), especially within the context of a "natural" situation.)

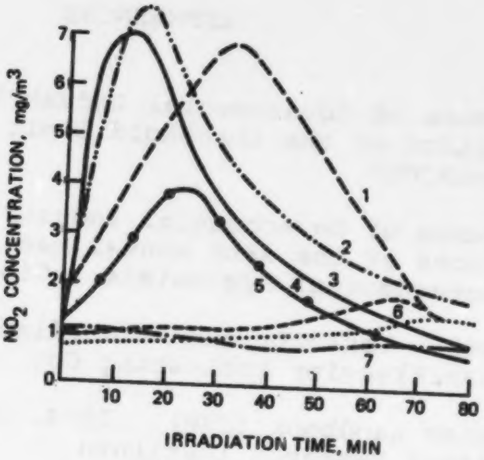


Figure 1. Dynamics of the conversion of nitrogen oxide to its dioxide in irradiated mixtures of various organic substances with nitrogen oxide. Legend: 1, THF; 2, hexene-1; 3, heptene-3; 4, furan; 5, cyclohexane; 6, benzene; 7, furfural. (Source: Popov, 1971.)

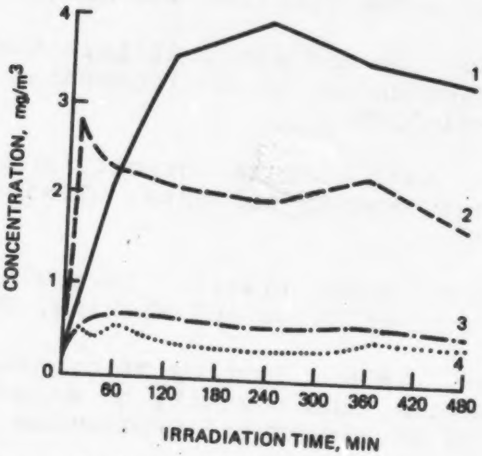


Figure 2. Dynamics of formation of acrolein and formaldehyde in irradiated mixtures of heptene and THF with nitrogen oxide. Legend: 1, acrolein from THF; 2, acrolein from heptene; 3, formaldehyde from THF; 4, formaldehyde. (Source: Popov, 1971.)

# REFERENCES

American Conference of Governmental Industrial Hygienists (ACGIH) 1971. Documentation of the threshold limit values, 3rd ed. Cincinnati, Ohio:ACGIH.

American Conference of Governmental Industrial Hygienists (ACGIH) 1976. Transactions of the 38th annual meeting of the American Conference of Governmental Hygienists. Cincinnati, Ohio:ACGIH.

Browning, E. 1965. Toxicity and metabolism of industrial solvents. Amsterdam:Elsevier Publishing Co.

Chemical Economics Handbook (CEH). 1974, 1975, 1977. Menlo Park, California:Stanford Research Institute.

Condensed Chemical Dictionary, 9th ed. 1977. New York: Van Nostrand Reinhold Co.

DiVincenzo GD, and Krasavage WJ. 1974. Serum ornithine carbamyl transferase as a liver response test for exposure to organic solvents. Am. Ind. Hyg. Assoc. J. 35:21.

Dunlop AP. 1967. Kirk-Othmer Encyclopedia of Chemical Technology Furfural. New York:Interscience Publishers. Vol 10:249.

Gleason MN, et al. 1969. Clinical toxicology of commercial products. Baltimore:The Williams and Wilkins Co.

JRB. 1979. Production and use profile:tetrahydrofuran. For the Office of Toxic Substances, US Environmental Protection Agency. (Contract No. 68-01-5105).

Kimura, ET et al. 1971. Acute toxicity and limits of solvent residue for sixteen organic solvents. Toxicol. Appl. Pharmacol. 19:699.

Lehmann, K.B. and F. Flury (1943). Toxicology and Hygiene of Industrial Solvents, Williams and Wilkins, Baltimore, Maryland.

MITRE Corporation. 1976. Scoring of organic air pollutants: chemistry, production, and toxicity of selected synthetic organic chemicals. For US Environmental Protection Agency (Contract No. 68-02-1495).

Muller, E. and J.K. Reichert (1969), Arch. Hyg. Bakt., 153(1), 26-32.

National Cancer Institute (NCI). 1979. Agenda:chemical selection working group. Conference held at NIH campus. May 24.

Popov VA. 1971. On experimental studies of photochemical oxidation of organic substances in the atmosphere. Gig. Sanit. 36(2):7.

Pozdnyakova AG. 1969. Hygienic standard for tetrahydrofuran in water bodies. Gig. Sanit. 34(9):114.

Shackelford WM, and Keith LH. 1976. Frequency of organic compounds identified in water. Athens, Georgia:Environmental Research Laboratory, US Environmental Protection Agency.

Slaga TJ et al. 1977. Skin-tumor-initiating ability of benzo(a) pyrene-7,8-did-9,10-epoxide (anti) when applied topically in tetrahydrofuran. Cancer Letter. 3(1-2):23-30.

Stanford Research Institute (SRI). 1978. Directory of Chemical producers USA. Menlo Park, California. p 250.

Stoughton, R.W. and B.H. Robbins (1936), Anaesthetic Properties of Tetrahydrofuran, J. Pharm. Exp. Therap., 58:171.

Survey of compounds which have been tested for carcinogenic activity, 1968-1969 volume. Prepared for the National Cancer Institute. PHS-149. (DHEW Publ No. (NIH) 72-35).

U.S. International Trade Commission. Imports of Benzenoid chemicals and products 1974-1977. Washington, D.C. US Government Printing Office.

Zapp, J.A., Jr., Personal communication to TLV Committee member, as cited by ACGIH (1971).

# CHEMICAL HAZARD INFORMATION PROFILE

## 2,4,6-Tribromophenol

Date of report: June 2, 1978

This chemical was chosen for study because several TSCA Section 8(e) submissions have been received on it and because of dioxin contamination found in analogous chlorine compounds.

The available information is not sufficient for judgment at this time. Additional information which will be obtained before making a judgment includes:

(1) Follow-up to 8(e) submitters requesting information on the composition and purity of tribromophenol flame retardants, with emphasis on potential dioxin contamination.

(2) Production volume from the TSCA inventory.

(3) Relevant information held by OPP--Tribromophenol has reported pesticide uses.

This CHIP will be revised and reevaluated based upon the additional information obtained.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

### Chemical Identity

Tribromophenol (TBP) is a white crystalline solid which melts at 95¼C. It has a penetrating odor, is insoluble in water, and is soluble in alcohol, chloroform, ether, and bases (CCD, 1971; Weast, 1971).

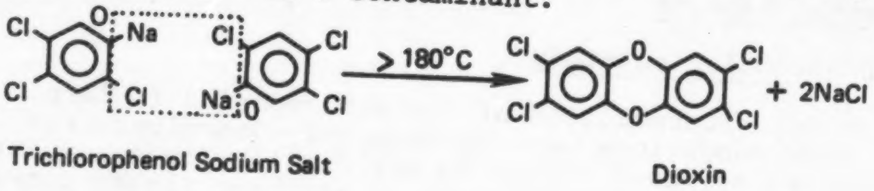
### Production and Use

The Directory of Chemical Producers (SRI, 1975) lists three manufacturers for TBP: Guardian Chemical Corp., Michigan Chemical Corp., and White Chemical Corp. No production volume data were found; however, inclusion in the Directory implies an annual production level of over 1,000 lb or value exceeding $1,000. The Chemical Buyer's Guide (1978) lists six additional sellers of TBP.

A variety of uses have been reported for TBP. It is used as an ingredient of pharmaceuticals and antiseptic germicides and as a fungicide (Stenger and Atchison, 1967). TBP has been reported to be an effective snail control agent (Steiner, 1971). Of greatest interest to OTS is TBP's use as a fire retardant. Great Lakes recommends TBP as a fire retardant on the following polymers and resins: acrylonitrile-butadiene-styrene (ABS), epoxy, phenolic, and polystyrene (Brooklyn Polytechnic Institute). Flammex 3BP reportedly contains TBP and is sold by a British firm (reference unknown). An analysis of Flammex 3BP showed that the product contained no dibenzodioxins or dibenzofurans, which are both highly toxic and are potential contaminants.

### Impurities

One of the major concerns is the close structural similarity to chlorophenol derivatives, which are used as herbicides. During the production of trichlorophenol, dioxin, a highly toxic compound, is formed as a contaminant.



Although one investigator stated that he did not find the bromine analog of dioxin in a sample of TBP fire retardant, further research is needed on the production process and possible contaminants of TBP.

## Health Aspects

### Toxicity

Little information concerning the toxicity of tribromophenol was found in Toxline or Toxback. However, there have been several Section 8(e) submissions concerning TBP.

The Merck Index (Stecher, 1960) reports that the oral rat $LD_{50}$ is 200 mg/kg; however, Patty (1963) cites an $LD_{50}$ of 2,000 mg/kg under similar conditions. TBP is rapidly absorbed from the gastroenteric tract and in an acute study induced pathological changes, such as congestion and hemorrhages, in the lungs. Moderate inflammation of the mucosa, stomach, and intestines was noted (Patty, 1963).

Like other halogenated phenols, TBP is capable of both uncoupling and inhibiting mitochondrial respiration in rat liver cells (Ratnikova and Yaguzhinskii, 1972; Stockdale and Selwyn, 1971).

The Section 8(e) submissions are summarized briefly below.

### 28-Day Subacute Dermal Toxicity Study on Albino Rats

TBP was slightly irritating to the skin and caused lesions at the skin test site. Body and organ weights and blood chemistry were normal. Based on changes in urine pH and specific gravity, one might suspect that TBP was absorbed in sufficient quantities to produce kidney damage. However, the data provided were inadequate to provide for an intelligent evaluation (8EHQ-1277-0024, 8EHQ-0278-0069).

### Pilot Teratology Study in Rats

The pilot study did not contain enough animals per dose group to be statistically valid. However, rats receiving 1,000 mg/kg/day had slight decreases in body weight between days 6 and 12 of gestation, an increase in postimplantation losses, and a slight decrease in the number of viable fetuses (8EHQ-0378-0095).

## Environmental Aspects

### Fish Accumulation Study

A 100-fold accumulation of TBP was reported in Carp. However, test conditions were inadequately described, the species chosen may have caused an artifically low accumulation value, and the decomposition products may have higher potential for accumulation. As stated in the current guidelines for "substantial risk," a 100-fold bioaccumulation is not considered a "substantial risk" (8EHQ-0178-0032).

## REFERENCES

Brooklyn Polytechnic Institute of New York, Department of Chemistry. Bromine Based Fire Retardants. Unpublished paper.

Condensed Chemical Dictionary (CCD), 8th ed. New York, Van Nostrand Reinhold Co. 1971.

OPD Chemical Buyer's Guide. New York, Schnell Publishing Co. 1978.

Patty, F. A. (ed.). Industrial Hygiene and Toxicology, vol. II. New York, Interscience Publishers. 1963. p. 1406.

Ratnikova, L. A., and L. S. Yaguzhinskii. Mechanism of the inhibition of mitochondrial respiration of the phenol type. Mitokhondrii 6:77, 1972. (Abstract)

SRI (Stanford Research Institute). Directory of Chemical Producers. Menlo Park, Calif. 1975.

Stecher, P. (ed.). The Merck Index, 7th ed. Rahway, N.J., Merck & Co., Inc. 1960.

Steiner, A. Snail Control Agents. Swiss Patent No. 510399, September 15, 1971.

Stenger, V. A., and G. H. Atchison. In Kirk-Othmer Encyclopedia of Chemical Technology, 2nd ed., vol. 3. New York, John Wiley and Sons. 1967. p. 778.

Stockdale, M., and M. J. Selwyn. Effects of ring substituents on the activity of phenols as inhibitors and uncouplers of mitochondrial respiration. Eur. J. Biochem. 21(4):565, 1971. (Abstract)

Weast, R. (ed.). Handbook of Chemistry and Physics, 52nd ed. Cleveland, Chemical Rubber Co. 1971.

# CHEMICAL HAZARD INFORMATION PROFILE

## Trichlorobutylene Oxide*

Date of report: January 3, 1978

This chemical was chosen for study because of its appearance in a technical journal advertisement, thus indicating some commercial significance, and its structural similarity to known carcinogens and mutagens. It is recommended that trichlorobutylene oxide (TCBO) be considered for testing, chiefly because of its structural similarity to known carcinogens and mutagens. TSCA Section 8(a) and 8(d) submissions should be required in order to supplement the very scanty information currently available.*

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

### Chemical Identity

Trichlorobutylene oxide (TCBO) is a dark amber liquid. It is miscible with organic solvents such as chloroform, benzene, and carbon tetrachloride; however, TCBO is insoluble in water. TCBO has a boiling point of 174°C, but will decompose at 155°C to form HCl under certain reaction conditions.

### Production and Use

It is not known whether TCBO is used commercially at this time. The only currently available information on the chemical consists of that supplied by Olin Chemicals, the only known producer. Olin, however, suggests a number of possible applications:

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*Subsequent to the review of this CHIP document and the selection of the tentative dispositions given above, the TSCA Interagency Testing Committee recommended halogenated alkyl epoxides for primary considerations for possible testing under Section 4(a) of TSCA (43 F.R. 16684). The EPA Administrator responded to this recommendations in 44 F.R. 2809528097.

(1) Urethanes--Chlorinated polyols (homopolymers of TCBO or copolymers of TCBO with ethylene oxide and/or propylene oxide) may be prepared. Polyols based on these formulations may increase the tensile strength, surface hardness, and fire retardancy of cast urethanes. Potential applications include surface coatings, laminated products, urethane elastomers, adhesives, and foams.

(2) Epoxy resins--TCBO may be cured directly into epoxy formulations, or the chemical may be prereacted with amines or alcohols and subsequently be formulated into epoxy compositions. TCBO addition to epoxy resins is reported to improve adhesive strength and flame retardancy. Epoxy products containing TCBO may be useful as adhesives, laminates, coatings, and castings.

(3) Esters--Acrylic esters can be formed by the reaction of TCBO with acrylic acid; these products may be polymerized with other olefins to yield chlorine-containing polymers. These ester intermediates may find use in lacquers, lubricants, paints and coatings, adhesives, and as flame retardants. Polyesters can be prepared from TCBO and adipic acid, maleic acid, etc., and possibly find use in laminates, adhesives, and fibers.

(4) Other applications--Suggested uses of TCBO and its derivatives include: polymerization into phenolic resins to improve flame retardancy; neutralizing agents; chemical intermediate; pesticides; polyurethane and epoxy catalyst; heavy-duty lubricant additive; solvents; olefinic polymerization activator; glycols; plasticizers; modifiers; novel resins; fire-retardant functional fluids; textiles; vulcanization of graft polymer rubbers.

## Health Aspects

The oral $LD_{50}$ of TCBO in rats is 1.5 g/kg. The rabbit acute dermal $LD_{50}$ ranges between 0.2 and 2.0 g/kg (abraded?); however, TCBO is a severe skin irritant in rabbits.

TCBO was found positive in the Ames test.

## Environmental Aspects

No information on the environmental fate or effects of TCBO was found in the sources consulted.

## REFERENCES

Olin Chemicals. Application Data: Uses and Chemistry of Trichlorobutylene Oxide (TCBO). Olin Corp. 1977.

Olin Chemicals. Product Data: Trichlorobutylene Oxide, Technical Grade. Olin Corp. 1977.

# CHEMICAL HAZARD INFORMATION PROFILE

## 1,1,2-Trichloroethane

Date of report: August 1, 1978

This chemical was chosen for study because it was found to be carcinogenic in an NCI bioassay.

It is recommended that 1,1,2-trichloroethane proceed to Phase I assessment. It is also recommended that TSCA Section 8(a) submissions be required for 1,1,2-trichloroethane. The available production/use information is very sketchy, thus making any exposure estimate difficult.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

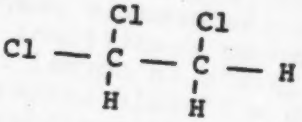
Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

Synonyms: Vinyl trichloride, ethane trichloride, beta trichloride

CAS No.: 79-00-5

Chemical Characteristics

The structure of 1,1.2-trichloroethane (1,1,2-TCE), $C_2H_3C_{13}$, is diagrammed below:



$$\begin{array}{ccccccc} & & \text{Cl} & & \text{Cl} & & \\ & & | & & | & & \\ \text{Cl} & - & \text{C} & - & \text{C} & - & \text{H} \\ & & | & & | & & \\ & & \text{H} & & \text{H} & & \end{array}$$

It is a colorless liquid which boils at 113.5°C and melts at -36.7°C. 1,1,2-TCE is slightly soluble in water and soluble in ethanol and ethyl ether (Deichmann et al., 1963).

Production and Use

There is a lack of conclusive evidence available concerning the production volumes of 1,1,2-TCE. In 1974, Dow Chemical and PPG Industries were the two producers of 1,1,2-TCE, and production estimates centered around 124 million lb (NCI, 1978). At present, Dow Chemical is the sole producer of 1,1,2-TCE, and several industry contacts have offered a 1978 production figure of 4 million lb (Mazella and Scott, 1978).

Originally, 1,1,2-TCE was used primarily as an intermediate in vinylidene chloride production; however, this use has been reportedly terminated by Dow Chemical (Mazella and Scott, 1978). Additional uses include use in adhesives, in the production of Teflon tubing, in lacquer, in coating formulations (NCI, 1978), and as a solvent for fats, waxes, natural resins, alkaloids, and other products (Mazella and Scott, 1978).

Health Aspects

Harms et al. (1976) observed significant increases in bile duct-pancreatic fluid and serum glutamate pyruvate transaminase (SGPT) activity in rats following IP injection of 1,800 mg/kg of 1,1,2-TCE. All rats treated with 1,1,2-TCE also exhibited centrilobular hepatic necrosis.

Klaassen and Plaa (1969) observed enhanced hepatic triglyceride levels in male rats only at near-lethal doses. There was no effect on lipid peroxidation at 0.75 for the $LD_{50}$ dose. The $LD_{50}$ by IP injection was 650 mg/kg. The $ED_{50}$ for liver dysfunction, as determined by diminution of phenolsulfonephthalein excretion, was 570 mg/kg. Necrosis was observed in both liver and kidneys.

Hanosono et al. (1975) studied the effects of an alloxan-induced diabetic state on the hepatic response in male rats. At 72 mg/kg IP, 1,1,2-TCE had no significant effect on SGPT activity or hepatic triglyceride levels in normal rats. In diabetic rats, however, this dose caused a 17-fold increase in SGPT activity and a 5-fold increase in hepatic triglycerides.

Watrous and Plaa (1972a, 1972b) determined nephrotoxicity by taking renal cortical slices from animals treated with 1,1,2-TCE and measuring the *in vitro* uptake of organic anions by the tissue. Significant depression of p-aminohippuric acid uptake occurred in the tissue of male mice that received 144 mg/kg (SC).

Klaassen and Plaa (1967b) investigated the susceptibility of male and female mice to the nephrotoxic effects of 1,1,2-TCE. The $ED_{50}$ for renal dysfunction, as determined by PSP excretion, was 240 mg/kg (IP) in male mice. Renal dysfunction could not be produced in females, even at lethal doses. The IP $LD_{50}$ was 490 mg/kg in males and 580 mg/kg in females.

Kronevi et al. applied 1,1,2-TCE directly on the skin of the backs of guinea pigs under anesthesia for periods of between 15 min and 12 hr. The epidermis showed morphological changes which continued to progress as exposure continued. The changes included pyknotic nuclei, perinuclear edema of basal and suprabasalar cells, and focal separation of the epidermis from the corium with vesicle formations. Six hours later, reduction of glycogen content and hydropic changes in the centrilobular area of liver tissue were noted, although 12 hr later the changes were less marked and in nonanesthetized animals they were absent. No morphological changes were noted in the kidney or the brain.

NCI (1978) conducted a bioassay of 1,1,2-TCE for possible carcinogenicity of Osborne-Mendel rats and B6C3F1 mice. Control groups were untreated or gavaged with corn oil, and low- and high-dose groups were gavaged with 1,1,2-TCE in corn oil. Dose levels were 42 and 92 mg/kg/day for rats and 195 and 390 mg/kg/day for mice. No convincing evidence was found for carcinogenicity of 1,1,2-TCE in Osborne-Mendel rats. The bioassay did provide evidence that 1,1,2-TCE is carcinogenic in B6C3F1 mice, causing hepatocellular carcinomas and adrenal pheochromocytomas.

Dermal contact with 1,1,2-TCE is dangerous because it is readily absorbed through the skin; however, most humans are exposed to 1,1,2-TCE through inhalation of vapors (NCI, 1978). OSHA has set forth a time weighted average standard of 10 ppm in air (NIOSH, 1975). The threshold limit value for substances in workroom air is also 10 ppm (ACGIH, 1975).

## Environmental Aspects

The 95-hr $LC_{50}$ for aquatic life (species unknown) is 10-100 ppm (NIOSH, 1975).

An EPA monitoring program has detected 1,1,2-TCE in ambient air in Louisiana, New Jersey, Texas, and California with concentrations ranging from 0.000036 $mg/m_3$ to 0.017 $mg/m_3$. The highest concentration of 1,1,2-TCE was found near a sanitary landfill in New Jersey (Pellerizi et al., 1976, 1977).

## REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). Documentation of TLV's. 1971. p. 263.

Deichmann, W. B. et al. In F. A. Patty (ed.), Industrial Hygiene and Toxicology, vol. 2. New York, John Wiley and Sons, Inc. 1963. p. 1290-1291.

Hanosono, George K. et al. Potentiation of the hepatotoxic responses to chemicals in alloxan-diabetic rats. Proc. Soc. Exp. Biol. Med. 149:903-907, 1975.

Harms, Molly S. et al. Increased "bile duct-pancreatic fluid" flow in chlorinated hydrocarbon-treated rats. Toxicol. Appl. Pharmacol. 35:41-49, 1976.

Klaassen, Curtis D., and Gabriel L. Plaa. Relative effects of various chlorinated hydrocarbons on liver and kidney function of dogs. Toxicol. Appl. Pharmacol. 10:119-131, 1967a.

Klaassen, Curtis D., and Gabriel L. Plaa. Susceptibility of male and female mice to the nephrotoxic and hepatotoxic properties of chlorinated hydrocarbons. Proc. Soc. Exp. Biol. Med. 124:1163-1167, 1967b.

Klaassen, Curtis D., and Gabriel L. Plaa. Comparison of the biochemical alterations elicited in livers from rats treated with carbon tetrachloride, chloroform, 1,1,2-trichloroethane and 1,1,1-trichloroethane. Biochem. Pharmacol. 18:2019-2027, 1969.

Kronevi, T., J. Wahlberg, and B. Holmberg. Morphological lesions in guinea pigs during skin exposure to 1,1,2-trichloroethane. Acta Pharmacol. Toxicol. 41(4):298-305, 1977.

Mazella, Angela, and Sari Scott. Production and Uses of 1,1,2-Trichloroethane. Contract No. EPA-68-01-3899. May 5, 1978.

NCI (National Cancer Institute). Bioassay of 1,1,2-Trichloroethane for Possible Carcinogenicity. DHEW Publ. No. (NIH) 78-1324. January 6, 1978.

NIOSH. Registry of Toxic Effects of Chemical Substances. 1975.

Pellerizi, E. D. et al. Monthly Technical Report Nos. 3, 9, and 12. Contract No. EPA 68-01-1228. 1976.

Pellerizi, E. D. et al. Monthly Technical Report Nos. 2, 8, and 11. Contract No. EPA 68-01-1228. 1977.

Watrous, William M., and Gabriel L. Plaa. Effect of halogenated hydrocarbons on organic ion accumulation by renal cortical slices of rats and mice. Toxicol. Appl. Pharmacol. 23:640-49, 1972a.

Watrous, William M., and Gabriel L. Plaa. The nephrotoxicity of single and multiple doses of aliphatic chlorinated hydrocarbon solvents in male mice. Toxicol. Appl. Pharmacol. 23:640-49, 1972b.

# CHEMICAL HAZARD INFORMATION PROFILE

## Trimellitic Anhydride

Date of report: March 3, 1978

Selection of this chemical for study was prompted by a NIOSH Current Intelligence Bulletin which reported rather severe respiratory problems in workers exposed to trimellitic anhydride (TMA) vapors. No additional information concerning the effects of TMA was found in the course of preparing this document.

It is recommended that EPA defer to NIOSH concerning action on TMA. This recommendation is made in light of the following considerations:

(1) The use pattern of TMA indicates that exposure is predominantly confined to the workplace.

(2) Due to its high reactivity, one would not expect significant environmental levels of TMA.

(3) The health aspects of TMA are well known to NIOSH.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

### Chemical Identity

Trimellitic anhydride (1,2,4-benzenetricarboxylic acid, 1,2-anhydride), $C_9H_4O_5$, is a combustible solid which melts at 164-166°C.

### Production and Use

Trimellitic anhydride (TMA) is derived from pseudocumene (Hawley, 1971). The Directory of Chemical Producers (SRI, 1976) lists Amoco Chemicals Corp. of Joliet, Ill., as the only U.S. manufacturer of the chemical. SRI estimates that this plant has a capacity of 50 million lb per year (EPA, 1977). The Chemical Week 1978 Buyers Guide Issue lists both Amoco Chemicals Corp. and Aldrich Chemical Co., Inc., as suppliers of trimellitic anhydride (McCurdy, 1977).

TMA is used as a curing agent for epoxy and other resins and in vinyl plasticizers, paints and coatings, polymers, polyesters, agricultural chemicals, dyes and pigments, pharmaceuticals, surface-active agents, modifiers, intermediates, and specialty chemicals (NIOSH, 1978).

The largest market for TMA is as an intermediate in the production of trimellitate plasticizers. The estimated 1976 production volume of trimellitate plasticizers is 30 million lb. These specialty plasticizers are used primarily in polyvinyl chloride resins where performance over a wide temperature range is necessary (EPA, 1977).

An estimated 7-8 million lb of TMA was consumed in 1976 for the production of alkyd (mainly water-based) and oil-free alkyd (polyester) surface coatings. TMA is also used to manufacture poly(amide-imide) and poly(ester-imide) resins. An estimated 2.3 million lb of these resins, which are used as wire enamels, was produced in 1976 (EPA, 1977).

## Health Aspects

### Toxicity

Rice et al. (1977) reported that two workers for a pipe-coating company developed pulmonary edema following exposure to a heated epoxy coating material. Exposure occurred during the spraying of an epoxy powder containing TMA as the curing agent onto pipes heated to 450°C. One worker developed symptoms after 3 weeks of employment, and the other after 6 weeks. Both workers showed similar patterns of cough, hemoptysis, and dyspnea. Lung functions returned toward normal within 1 month of exposure termination.

Yeiss et al. (1977) investigated illnesses in workers involved in TMA manufacture. Data on 14 workers suggested three distinct syndromes induced by TMA inhalation:

(1) Development of rhinitis or asthma after a latent exposure period of weeks to years. Sensitized workers then exhibited symptoms immediately following exposure.

(2) Onset of cough and dyspnea 4-8 hr after a work shift. This syndrome also appeared to involve a latent exposure period. Respiratory symptoms were usually accompanied by malaise, chills, fever, and muscle and joint aches ("TMA-flu"). This reaction was associated with high-dose exposure to TMA.

(3) Irritant effect characterized by rhinorrhea, epistaxis, cough, dyspnea, and wheezing. No latent period was associated with this effect.

Fawcett et al. (1977) also observed the aforementioned sensitization effect in workers exposed to TMA.

## Exposure

A NIOSH Health Hazard Evaluation of a paint and varnish company which manufactures an epoxy paint found an average airborne concentration of 1.5 $mg/m^3$ TMA during processing operations and 2.8 $mg/m^3$ TMA during decontamination.

In a plant using TMA-epoxy powder pipe coatings, TMA concentrations ranged from 11 to 27 $mg/m^3$ (Department of Labour, Canada).

NIOSH (1978) estimates that approximately 20,000 American workers are at risk of exposure to TMA. There is no OSHA standard for TMA. Amoco Chemicals Corp. (1976) suggests a limit of 0.05 $mg/m^3$.

## Environmental Aspects

No information was found concerning the fate and effects of TMA in the environment. Because of its chemical structure, one would expect TMA to be rapidly hydrolyzed to trimellitic acid in aquatic systems.

## REFERENCES

Amoco Chemicals Corp., Environmental Health Services, Medical and Health Services Dept. Amoco -- Industrial Hygiene Toxicology and Safety Data Sheet. July 8, 1976.

Department of Labour, Alberta, Canada. Report to NIOSH. (As cited in NIOSH, 1978)

Fawcett, I. W., A. J. Taylor, and J. Pepys. Asthma due to inhaled chemical agents -- epoxy resin systems containing phthalic acid anhydride, trimellitic acid anhydride and triethylene tetramine. Clin. Allergy 7(1):1-14, 1977.

Hawley, G. G. (ed.). The Condensed Chemical Dictionary, 8th ed. New York, Van Nostrand Reinhold Co. 1971.

McCurdy, P. P. (ed.). Chemical Week 1978 Buyers Guide Issue. New York, McGraw-Hill, Inc. 1977.

NIOSH. Current Intelligence Bulletin 21, Trimellitic Anhydride (TMA). DHEW (NIOSH) Publ. No. 78-121. 1978.

NIOSH. Health Hazard Evaluation Determination Report No. 74-111-283. (As cited in NIOSH, 1978)

Rice, D. L., D. E. Jenkins, J. M. Gray, and J. D. Greenberg. Chemical pneumonitis secondary to inhalation of epoxy pipe coating. Arch. Environ. Health, July/August 1977, p. 173-178.

SRI (Stanford Research Institute). Directory of Chemical Producers. Menlo Park, Calif. 1976.

U.S. Environmental Protection Agency. A Study of Industrial Data on Candidate Chemicals for Testing. EPA 560/5-77-006, PB 274264. 1977.

Yeiss, C. R., R. Patterson, J. J. Pruzansky, M. M. Miller, M. Rosenberg, and D. Levitz. Trimellitic anhydride induced airway syndromes: Clinical and immunologic studies. J. Allergy Clin. Immunol. 60(2):96-103, 1977.

## CHEMICAL HAZARD INFORMATION PROFILE

### Vinyl Bromide

Date of report: January 30, 1978

This chemical was chosen for study because of its structural similarity to the carcinogen vinyl chloride and its use in special fire-resistant polymers.

It is recommended that vinyl bromide proceed to Phase I assessment. Results of a rat inhalation study (8EHQ-0479-0281) indicate an increased incidence of angiosarcomas at all levels tested. A study to determine residual vinyl bromide levels in fabric and fiber samples did not detect vinyl bromide in any samples at a detection limit of 0.04 ppm.

This information will be forwarded to CPSC on an FYI basis.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

## CHEMICAL HAZARD INFORMATION PROFILE

### Vinyl Fluoride

Date of report: January 30, 1978

This chemical was chosen for study because of its structural similarity to the carcinogen vinyl chloride and its use in special fire-resistant polymers.

The following recommendations are made regarding further OTE evaluation of the possible health or environmental hazards of vinyl fluoride:

(1) Refer to EPA-ORD for mutagenicity testing--No mutagenicity data are currently available.

(2) Require TSCA Section 8(d) submissions--No information on chronic studies is readily available.

(3) Check with FDA and NIOSH for additional information--FDA has apparently evaluated the safety of polyvinyl fluoride for use in food packaging. NIOSH has scheduled a criteria document on vinyl compounds for FY 78.

(4) Update this Chemical Hazard Information Profile based on the above information.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

## CHEMICAL HAZARD INFORMATION PROFILE

### Vinylidene Bromide

Date of report: January 30, 1978

This chemical was chosen for study because of its structural similarity to the suspected carcinogen vinylidene chloride and its possible use in special fire-resistant polymers.

It is recommended that judgment on this chemical be deferred until review of the TSCA inventory allows a determination of its commercial significance. The disposition of this CHIP will be reconsidered when the inventory has been checked.

This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

# CHEMICAL HAZARD INFORMATION PROFILE

## Vinylidene Fluoride

Date of report: January 30, 1978

This chemical was chosen for study because of its structural similarity to the suspected carcinogen vinylidene chloride and its possible use in special fire-resistant polymers.

It is recommended that TSCA Section 8(d) submissions be required for this chemical because the available information was generally sparse. Of particular concern is a total lack of information on chronic toxicity. This CHIP will be updated based upon any additional information obtained. If no data are identified, testing should be considered.

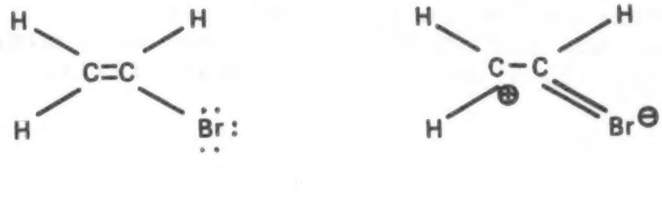
This report represents a preliminary investigation of the subject chemical's potential for injury to human health and the environment. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, it necessarily follows that this report may not reflect all available information on the subject chemical.

Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

### Chemical Identity

#### Vinyl Bromide

Vinyl bromide ($HBrC{=}CH_2$) is a colorless gas with a molecular weight of 106.96. Synonyms for vinyl bromide include bromoethylene and bromoethene. Vinyl bromide melts at -139.54°C and boils at 15.6°C. Its liquid density at 20°C and saturation pressure is 1.4933 g/ml. Vinyl bromide is combustible with air and presents an explosion hazard at moderate concentrations. It is considered insoluble in water, but soluble in alcohol, acetone, benzene, and chloroform. Vinyl bromide has relatively low reactivity. This is attributed to resonance involving a polarized structure:



The resonance effect is such that the bond between the bromine atom and the carbon atom has the characteristics of a double bond. The bromine atom thus is less labile than it would be if the bond were purely of a single-bond nature. Vinyl bromide undergoes polymerization and copolymerization. The bromine atom is relatively unreactive in nucleophilic substitution reactions. Vinyl bromide undergoes many reactions typical of olefins (Braker and Mossman, 1971).

### Vinyl Fluoride

Vinyl fluoride ($HFC=CH_2$) is a colorless gas with a mild odor. The molecular weight of vinyl fluoride is 46.05. Synonyms for vinyl fluoride include fluoroethylene and fluoroethene. Vinyl fluoride melts at -160.5°C and boils at -72.2°C. The liquid density of vinyl fluoride at 10°C and saturation pressure is 0.6808 g/ml. It is considered insoluble in water and soluble in ethyl alcohol, acetone, and ethyl ether. Vinyl fluoride is flammable in air at concentrations between 2.6 and 21.7%. The net reactivity of vinyl fluoride is decreased by the electron-attracting effect of the fluorine atom so that it is less reactive toward addition of hydrogen halides than ethylene, even though the effect is not strong enough to determine the direction of addition (Braker and Mossman, 1971).

### Vinylidene Bromide

Vinylidene bromide ($H_2C=CBr_2$) has a molecular weight of 185.85. (It is a liquid with a boiling point of 92°C. Its specific gravity is 2.1780. This information, which is from the Preliminary Early Warning Report, has not been confirmed for this report.)

### Vinylidene Fluoride

Vinylidene fluoride ($H_2C=CF_2$) is a colorless gas with a faint ethereal odor. Vinylidene fluoride boils at -83°C and melts at -144°C. The liquid density at 23.6°C is 0.617 g/ml. Its molecular weight is 64.04. Vinylidene fluoride presents a fire risk since it is flammable at concentrations in air between 5.5 and 21.3% by volume. It forms peroxides on exposure to pure oxygen. Vinylidene fluoride is slightly soluble in water. It is soluble in ethyl alcohol and very soluble in ether. Synonyms for vinylidene fluoride include vinylidene difluoride, Genetron 1132A, 1,1-difluoroethylene, and 1,1-difluoroethene. Vinylidene fluoride also retains the ethylene characteristic of small molecular volume and a flat two-dimensional molecular shape (Burgison et al., 1955; Braker and Mossman, 1971).

## Production and Use

### Vinyl Bromide

Vinyl bromide can be produced by hydrobromination of acetylene in the presence of catalysts or by partial debromination of ethane dibromide with alcoholic potassium hydroxide (Braker and Mossman, 1971). Commercial manufacturers of vinyl bromide include Dow Chemical and Ethyl Corp. (Brine Products Division) (SRI, 1975). It is used as an intermediate in organic synthesis and for the preparation of plastics by polymerization and copolymerization. The major use of vinyl bromide is in the production of flame-retardant synthetic fibers. An example of this is SEF, a modacrylic fiber produced by Monsanto. The formula for SEF is 79 to 81% acrylonitrile, 9% vinyl bromide, 8% vinylidene chloride, and 2 to 4% other. SEF is used primarily in children's sleepwear. It is produced in a batch polymerization operation with a suspension polymerization medium and a wet spinning process (SRI, 1976). This method of production would probably preclude residual vinyl bromide monomer in the finished product. Dow Badische Co. estimated (in 1976) its use of vinyl bromide at 100,000 to 1.5 million lb annually. They have used it since 1970.

### Vinyl Fluoride

Vinyl fluoride is produced from acetylene and hydrogen fluoride in the presence of mercury catalysts. Another method is the addition of hydrogen fluoride to acetylene to form 1,1-difluoroethane, followed by pyrolysis to vinyl fluoride (Braker and Mossman, 1971). Vinyl fluoride is produced by E. I. du Pont de Nemours and Co., Inc. (SRI, 1975). Since 0.6 lb of acetylene is used to produce 1 lb of vinyl fluoride, and less than 2 million lb of acetylene is consumed by this industry, the production maximum is 3.3 million lb of vinyl fluoride per year (SRI, 1975). Vinyl fluoride's primary use is as a chemical intermediate to make polyvinyl fluoride (Teldar) film. Vinyl fluoride has been in use by E. I. du Pont de Nemours and Co. since 1962.

Polyvinyl fluoride film is characterized by superior resistance to weather, high strength, and a high dielectric constant. It is used as a film laminate for building materials and in packaging electrical equipment. Polyvinyl fluoride film poses a hazard, so it is not recommended for food packaging. Polyvinyl fluoride evolves toxic fumes upon heating (Hawley, 1977).

### Vinylidene Bromide

Vinylidene bromide does not appear to be produced in commercial quantities for any use by any manufacturer.

### Vinylidene Fluoride

Vinylidene fluoride can be made by various production procedures based on pyrolysis. Commercial procedures include production of vinylidene fluoride in 43% yield by passing a mixture of 6 moles of hydrogen and 33 moles of $CF_2ClCH_2Cl$ over nickel wire at 490-500°C with a contact time of 10 sec. It has also been obtained by the dehydrochlorination of $CF_2ClCH_3$ (Braker and Mossman, 1971) and by dechlorination of $CH_2ClCF_2Cl$ (SRI, 1976). Vinylidene fluoride is produced by E. I. du Pont de Nemours and Co. and Scientific Gas Products, Inc. (SRI, 1975). Vinylidene fluoride is used in the formulation of many polymers and copolymers such as perfluoropropylene-vinylidene fluoride (Viton , Fluorel ), chlorotrifluoroethylene-vinylidene fluoride (Kel F ), polyvinylidene fluoride, and hexafluoropropylene-tetrafluoroethylene-vinylidene fluoride. It is also used as a chemical intermediate in organic synthesis (Standen, 1966).

Polyvinylidene fluoride is suitable for compression and injection molding and extrusion. Because of its thermal characteristics (melting point, 340°F), polyvinylidene fluoride (and polymers containing vinylidene fluoride) can be used in insulation for high-temperature wire and in aircraft missiles. Polyvinylidene fluoride is also used in tank linings, chemical tanks, tubing, and protective paints and coatings (imparting exceptional--30 year--resistance to weathering and ultraviolet light), in impeller parts, shrinkage tubing (to protect resistors and diodes), and as a soldering joint sealant (Hawley, 1977).

## Health Aspects

### Vinyl Bromide

Vinyl bromide is considered a moderately toxic substance. The threshold limit value in air is 250 ppm (NIOSH, 1976), although a 50-ppm TLV is suggested by other sources (Braker and Mossman, 1971). The $LD_{50}$ for rats is 500 mg/kg (NIOSH, 1976). In high concentrations, vinyl bromide may produce dizziness, disorientation, and sleepiness in humans. Vinyl bromide has been found to be mutagenic to Salmonella typhimurium (strains TA1535 and TA100) using the Ames Salmonella/microsome test (Vincent Simmons and Dennis Pool, Stanford Research Institute, unpublished). In another study, vinyl bromide and its presumed metabolites have been shown to be strong mutagens in Salmonella typhimurium (Malavell, Bartsch, and Montesono, unpublished; referred to by Barbin, 1975).

Vinyl bromide given orally as a 50% solution in corn oil has an $LD_{50}$ of about 500 mg/kg in rats. It was not irritating to the intact or abraded skin of rabbits, but produced slight to moderate eye irritation. In acute inhalation studies, 100,000 ppm killed rats in 15 min, but if exposure was halted prior to death the animals recovered completely. Exposure to 50,000 ppm produced unconsciousness in rats in 25 min. All rats survived 1.5 hr of exposure, but not all survived after 7 hr of exposure. Those animals that survived 50,000 ppm were sacrificed 2 weeks after exposure. Slight to moderate damage to the liver and kidneys was observed after this exposure. Rats exposed to 25,000 ppm vinyl bromide were anesthetized, but all survived for 7 hr at this level with no abnormalities (Leong and Torkelson, 1970).

In chronic exposure studies, rats inhaling an atmosphere containing 10,000 ppm vinyl bromide for 7 hr per day, 5 days per week for 4 weeks became hypoactive and drowsy within 1 hr after each initiation of exposure, thereafter remaining motionless in their cages for the duration of the exposure (Leong and Torkelson, 1970).

The rapid onset and recovery of exposed animals from vinyl bromide's anesthetic effects has led some researchers to suspect that vinyl bromide is rapidly absorbed by and excreted from the lungs. On removal, the animals rapidly recovered from drowsiness and became quite active. The recovery time after treatment became progressively longer as the experiment progressed. After 15 days of exposure, a decrease in weight gain was observed. The researchers believed that this was due to decreased feeding activity. On necropsy of a single moribund rat, which was sacrificed on the 9th day, gross multifocal gray areas were observed in the lungs; there were no other gross changes in any other organs of sacrificed rats. In general the lungs of the sacrificed rats did not show compound-related changes (Leong and Torkelson, 1970).

In a more extensive set of studies, rats, rabbits, and monkeys were exposed to 250 or 500 ppm vinyl bromide for 6 hr per day, 5 days per week for 6 months. There were no compound-related effects with respect to demeanor, body and organ weight, food consumption, a number of hematological parameters, or mortality. Gross and microscopic examination of the major organs and tissues revealed no remarkable abnormal changes. All species experienced minor insignificant decreases in weight gains compared with controls. There was a dose-related increase in nonvolatile blood bromine. All species suffered a somewhat high rate of miscellaneous lung abnormalities; patchy consolidation and blanched spots of lung tissue were observed in male rats at 500-ppm level of exposure (this was not statistically significant). No other organs displayed any pathological effects. Male rabbits showed insignificant increases in the thyroid weight/body weight ratio at both dosage levels; insignificant increases were seen in the liver weight/body weight ratio in female monkeys and spleen weight/body weight ratios in male and female monkeys at both the 250- and 500-ppm levels. No histological changes were found in these organs. The heart weight/body weight ratios for both sexes and the liver weight/body weight ratios for male rats in 250-ppm exposure group were significantly higher than values for corresponding control animals (this was not seen at 500 ppm). On the basis of their work, these researchers recommended that repeated exposure to vinyl bromide not exceed 500 ppm (with a time weighted average of 250 ppm) (Leong and Torkelson, 1970).

Vinyl bromide has been tested for activity as a fumigant by measuring mortality in naked eggs and mature larvae of fruit flies 48 hr after a 2-hr exposure. The $LD_{50}$ was found to be greater than 155 mg/l; therefore, vinyl bromide was judged to be an ineffective fumigant (Burditt et al., 1963).

In another inhalation study, male rats were exposed to 2% vinyl bromide 4 or 5 hr per day for 1, 2, 5, or 10 consecutive days. This treatment was also combined with administration of sodium phenobarbital (PB) and/or administration of potassium bromide in the drinking water. Vinyl bromide exposure caused significant weight loss during the first few days (weight loss was amplified by administration of PB). The weight loss was usually due to depression and resulting decreased food intake (as revealed by pair feeding studies). Behavioral depression may be attributed to the anesthetic effect of vinyl bromide and the depressant effect of bromide ion (a known central nervous system depressant), whose liberation was greatly accelerated by phenobarbital. Rats receiving PB along with the vinyl bromide treatment lost more weight than could be accounted for in pair feeding studies.

The toxicity of vinyl bromide appeared as injury to the liver, seen during the first 24 to 48 hr of exposure. Repair of this damage was completed by the 5th day after exposure. Resumption of weight gain corresponded to recovery from liver damage. Hepatic injury may result from the formation of alkylating agents from vinyl bromide through the action of liver microsomes. Vinyl bromide alone did not cause liver aberrations observable by light microscope. Those animals subjected to PB and vinyl bromide showed accentuation of hepatic lobular markings. Several grayish white foci measuring 0.1 to 1 cm were observed in one rat liver observed after 2 days of exposure. Some rats experienced moderate congestion of the lungs (Van Stee et al., 1977).

Vinyl bromide has been studied in a mouse liver microsome system. A mixture of vinyl bromide in air [the report contains conflicting statements of "vinyl bromide/air" and "vinyl bromide in oxygen (50% by volume)"] was sucked through a medium of liver microsomes prepared from phenobarbitone-pretreated male mice. Resultant volatile alkylating metabolites were trapped by reaction with 4-(4-nitrobenzyl) pyridine (NBP). The absorption spectra of the trapped products were identical with those obtained by reaction of chloroethylene oxide with NBP. The results of this experiment suggest that vinyl bromide is converted by microsomal enzymes into the corresponding epoxide, which in this experiment reacted with NBP. Identification of a metabolic product of vinyl bromide similar to chloroethylene oxide implies that vinyl bromide's mutagenic properties may be due to rearrangements similar to those which chloroethylene oxide undergoes (chloroethylene oxide has the capacity to rearrange to 2-chloroacetaldehyde. Both chloroethylene oxide and chloroacetaldehyde can bind covalently to nucleophilic centers such as adenosine) (Barbin et al., 1975).

### Vinyl Fluoride

Vinyl fluoride is considered nontoxic; however, when it reaches high concentrations, the oxygen content of the air can reach a critically low level. The approximate lethal concentration of vinyl fluoride to most animals has been estimated at 800,000 ppm (Cook and Pierce, 1973). Rats exposed to air containing 20% vinyl fluoride for 30 min showed no noticeable effects (Braker and Mossman, 1971). At 30% by volume in air, vinyl fluoride causes slight intoxication. Rats lost their postural reflex at 60% and lost the righting reflex at 70% vinyl fluoride in air. Eighty percent vinyl fluoride caused rats to show slight intoxication and labored breathing (possibly due to insufficient oxygen). Corneal reflex was retained by rats exposed to 80% vinyl fluoride for 12.5 hr (Patty, 1963).

Rats were exposed to 3,000 ppm vinyl fluoride for 30 min. The rats experienced significant mild diuresis. They showed an increased fluoride ion excretion 4 to 6 days after exposure. There was no statistically significant increase in creatinine or sodium ion excretion. Potassium elimination was elevated on the 5th day. These animals showed no significant difference in growth rates, nor did they show gross pathological changes except in the kidney (Dilley et al., 1974) (see "Biological Aspects, Vinylidene Fluoride," for kidney description).

Vinyl fluoride gas was bubbled through a 2% suspension of rabbit erythrocytes in saline at a rate of 150 ml/min (150 bubbles/min) for 10 min. The reaction vessel was then sealed for 18 hr. The erythrocytes were observed to be crenated after 10 min of exposure, the absorption maxima of the rabbit hemoglobin were slightly altered, and the electrophoretic characteristics of the RBC hemoglobin were slightly altered. The cells returned to their "normal" color within 0.5 min of reexposure to air (Pennington and Fuerst, 1971).

### Vinylidene Bromide

Vinylidene bromide has been tested in fed and fasted rats for short-term inhalation toxicity by measuring survival 24 hr after a 4-hr exposure period. The vapors were respiratory tract irritants; they presumably contained HBr gas, a known irritant which the researchers suspect may have caused the observed injury and death. The no-effect concentration was set at 46 ppm, since neither the fed nor the fasted rats died at this exposure level. At 98 ppm, two of five fasted rats died; none of five fed rats died. At 471 ppm, three of five fed and five of five fasted rats were killed. The probable cause of death was acute pulmonary edema and hemorrhage (Jaeger et al., 1975).

### Vinylidene Fluoride

Vinylidene fluoride is considered toxic by inhalation (Hawley, 1977). The lowest lethal concentration is 128,000 ppm for a 4-hr exposure (NIOSH, 1976). Vinylidene fluoride has been reported to be nontoxic to rats at 800,000 ppm (Jaeger et al., 1975, refer to Lester Greenberg, Acute and chronic toxicity of some halogenated derivatives of methane and ethane, Arch. Ind. Hyg. Occup. Med. 2:335-344, 1950).

Exposure of rats to levels of vinylidene fluoride ranging from 40% by volume to 80% (in oxygen) caused the animals to show an unsteady gait but no loss of reflexes. Exposure was continued for 19 hr. There were no progressive signs of intoxication. These animals showed no signs of pulmonary irritation upon sacrifice and examination (Patty, 1963).

Rats were exposed to 2,200 ppm vinylidene fluoride for 30 min. These rats showed a significant increase in urinary excretion of fluoride within 24 hr of exposure and again 4 to 6 days after exposure. They had a statistically nonsignificant increase in urine volume. Potassium excretion rose for at least 1 day. Creatinine and $Na^+$ elimination showed no significant change, and growth rates were not altered.

Upon sacrifice, no significant pathological changes were noted except in the kidney. The renal medulla of the kidney showed marked hyperemia, and there was a pale whitish band in the cortex near the corticomedullary junction. The midcortical area sometimes showed ischemic-appearing areas. These changes were most pronounced on the 3rd and 4th postexposure days and were almost absent after 2 weeks. Fluoride ion is known to affect kidney function by interfering with the proximal tubules of the kidneys. The increase in fluoride excretion tends to support the hypothesis that many fluoride-containing compounds are biodegradable. The cylic excretion of fluoride suggests that fluorocarbons or one of their metabolites are being stored in a compartment with a 5-day turnover rate (Dilley et al., 1974).

A 4-hr exposure of fed and fasted rats to ~27,000 or ~82,000 ppm vinylidene fluoride caused no deaths within 24 hr of exposure. It was not observed to be hepatotoxic (Jaeger et al., 1975).

Another inhalation study on the lethal concentration of vinylidene fluoride reported that, at the 4-hr exposure level, 128,000 ppm killed two of six or three of six rats (four of six in a static study). These researchers ranked it as a "slight hazard" (rank second in a classification system that went from a low of 1 to a high of 19) (Carpenter et al., 1949). Vinylidene fluoride retains ethylene's inability to sensitize the heart to epinephrine (as opposed to chlorination of ethylene, which produces compounds that cause sensitization and multifocal ectopic ventricular beats) (Burgison et al., 1955).

Rabbit erythrocytes suspended in saline were exposed to vinylidene fluoride gas which was bubbled through the medium for 10 min. These cells showed crenation and reduction in size. They showed no change in electrophoretic characteristics after 10 min of exposure. The erythrocyte suspension was then held in the sealed reaction vessel for 18 hr. The solution returned to its original color immediately upon reexposure to air (Pennington and Fuerst, 1971).

## Environmental Aspects

No data on the probable environmental fate and effects of these compounds have been found in the literature. The low water solubility of these compounds suggests that aquatic contamination is improbable. Their release into the atmosphere seems unlikely except in the case of a rare accidental spill or unless one of the polymers contains an abnormally large amount of the unreacted monomer. Hence, the potential environmental threat posed by these materials is probably low.

## APPENDIX. Pyrolysis of Polymers Containing Vinylidene Fluoride

Pyrolysis products of polymers containing vinylidene fluoride and hexafluoropropene were found to be less toxic than those of polytetrafluoroethylene (Teflon ) (Carter et al., 1974). Three compounds were considered: a copolymer of vinylidene fluoride and hexafluoropropene ($VF_2/HFP$); a copolymer of vinylidene fluoride and hexafluoropropene with "additives to provide improved properties," ($VF_2/HFP$-A); and a tetrafluoroethylene ($VF_2/HFP/TFE$). The studies were conducted on groups of 10 male (225 to 250 g) Sprague-Dawley rats in a 142-liter chamber, with a 30-min exposure period. These polymers were found to be similar in their thermal degradation characteristics.

Complete thermal degradation of these polymers occurs at 525-550°C. The $LD_{50}$ for $F_2/HFP$ is 2.36 g of the polymer pyrolyzed in the chamber at 550°C. The $LD_{50}$ for $VF_2/HFP/TFE$ is 1.52 g; $VF_2/HFP$-A has an $LD_{50}$ of 1.06 g. For 800°C pyrolysis, the $LD_{50}$'s are as follows: 0.59 g for $VF_2/HFP$; 0.42 g for $VF_2/HFP/TFE$;

0.46 g for $VF_2$/HFP-A. The $VF_2$/HFP pyrolysate appears to be the least toxic. Death due to exposure generally occurred within 48 hr. Most animals died from 4 to 24 hr postexposure, but no animals died during exposure. Gross and histological examination of tissues from the rats exposed to lethal levels of the pyrolysates revealed lesions characteristic of the response following exposure to severe pulmonary irritants. This response was characterized by initial capillary damage leading to pulmonary edema, with accompanying alveolar cell hypertrophy and desquamation. If the animal survived, the lungs returned to normal within 1 week of exposure. No other organ system was found to have been affected by the exposure, including the renal system. The exact composition of the pyrolysate fumes was not stated.

## REFERENCES

Barbin, A. et al. Liver-microsome-mediated formation of alkylating agents from vinyl bromide and vinyl chloride. Biochem. Biophys. Res. Commun. 67(2):596-603, 1975.

Braker, William, and Allen Mossman. Matheson Gas Data Book, 5th ed. New Jersey, Matheson Gas Products. 1971.

Burditt, Arthur K. et al. Screening of fumigants for toxicity to eggs and larvae of the Oriental fruit fly and Mediterranean fruit fly. J. Econ. Entomol. 56(3):261-265, 1963.

Burgison, Raymond M. et al. Anesthesia. XLVI. Fluorinated ethylenes and cardiac arrhythmias induced by epinephrine. J. Pharmacol. Exp. Ther. 114:470-472, 1955.

Carpenter, Charles P. et al. The assay of acute vapor toxicity, and the grading and interpretation of results on 96 chemical compounds. J. Ind. Hyg. Toxicol. 31(6):343-346, 1949.

Carter, V. L. et al. The acute inhalation toxicity in rats from the pyrolysis products of four fluoropolymers. Toxicol. Appl. Pharmacol. 30:369-376, 1974.

Cook, E. W., and J. S. Pierce. Toxicology of fluoroolefins. Nature 242(5396):337-338, 1973.

Dilley, James V. et al. Fluoride ion excretion by male rats after inhalation of one of several fluoroethylenes or hexafluoropropene. Toxicol. Appl. Pharmacol. 27:582-590, 1974.

Hawley, Gessner G. (ed.). The Condensed Chemical Dictionary, 9th ed. New York, Van Nostrand Reinhold Co. 1977.

International Technical Information Institute. Toxic and Hazardous Industrial Chemicals Safety Manual. Tokyo. 1976.

Jaeger, Rudolph J. et al. Short-term inhalation toxicity of halogenated hydrocarbons. Arch. Environ. Health 30(1):26-31, 1975.

Leonard, Edward (ed.). Vinyl and diene monomers, part 3. In High Polymers XXIV. New York, Wiley-Interscience, Publishers. 1971.

Leong, B. K., and T. R. Torkelson. Effects of repeated inhalation of vinyl bromide in laboratory animals with recommendations of industrial handling. Am. Ind. Hyg. Assoc. J. 31(1):1-11, 1970.

NIOSH. Registry of Toxic Effects of Chemical Substances, 1976 ed.

Patty, Frank A. (ed.). Industrial Hygiene and Toxicology, 2nd ed., vol. 2. New York, Interscience Publishers, Inc. 1963.

Pennington, K., and R. Fuerst. Biochemical and morphological effects of various gases on rabbit erythrocytes. Arch. Environ. Health 22(4):476-481, 1971.

Sax, Irving N. Dangerous Properties of Industrial Materials, 3rd ed. New York, Van Nostrand Reinhold Co. 1968.

Standen, Anthony (exec. ed.). Kirk-Othmer Encyclopedia of Chemical Technology, 2nd ed. New York, Interscience Publishers.

Stanford Research Institute (SRI). Chemical Economics Handbook. Menlo Park, Calif. 1976.

Stanford Research Institute (SRI). Directory of Chemical Producers. Menlo Park, Calif. 1975.

Stecher, Paul (ed.). The Merck Index, 8th ed. Rahway, N.J., Merck and Co., Inc. 1968.

Van Stee, E. W. et al. Studies in the inhalation toxicology of vinyl bromide. To be published in Toxicol. Appl. Pharmacol., 1977.

Weast, Robert C. (ed.). CRC Handbook of Chemistry and Physics, 52nd ed. Cleveland, The Chemical Rubber Co. 1971.

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